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#### (54) Title: LAMININ 2 AND METHODS FOR ITS USE

(54) Titre: LAMININE 2 ET SES METHODES D'UTILISATION

#### (57) Abstract

The present invention provides substantially purified laminin 2, methods for making recombinant laminin 2, cells that express recombinant laminin 2, and methods for using the substantially purified laminin 2 to accelerate peripheral nervous system nerve regeneration, and to promote cell attachment and migration.

#### (57) Abrégé

La présente invention concerne une laminine 2 sensiblement purifiée, des méthodes de construction d'une laminine 2 de recombinaison, des cellules exprimant ladite laminine 2 de recombinaison, ainsi que des méthodes d'utilisation de la laminine 2 sensiblement purifiée visant à accélérer la régénération des nerfs du système nerveux périphérique et à favoriser la fixation et la migration cellulaires.

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A61K 38/39, A61P 9/00, 21/00, 25/00, A61L 31/00  (21) International Application Number: PCT/US00/11378 (22) International Filing Date: 28 April 2000 (28.04.00)  (22) International Filing Date: 28 April 2000 (28.04.00)  (23) Priority Data: 28 April 2000 (28.04.00)  (30) Priority Data: 60/131,720 30 April 1999 (30.04.99) US 60/139,198 15 June 1999 (15.06.99) US 60/143,289 12 July 1999 (12.07.99) US 60/155,945 24 September 1999 (24.09.99) US 60/155,945 24 September 1999 (24.09.99) US 60/155,945 24 September 1999 (24.09.99) US 60/155,945 29 REPLATED BY APPLICATION OF MEDICINE AND DENTISTRY OF NEW JERSEY ROBERT WOOD JOHNSON MEDICAL SCIIOOL [US/US]; Piscataway, NJ 08854 (US).  (43) International Publication Date: 9 November 2000 (09.11.0)  (81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RS, SE, SG, SI, SK, SL, TI, TM, TR, TT, TZ, UA, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KA, BY, KG, KZ, MD, RU, TJ, TM), European patent (ABE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LM, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LM, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LM, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LM, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LM, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LM, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LM, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LM, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LM, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LM, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LM, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LM, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LM, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LM, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LM, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LM, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LM, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LM, CY, DE, DK, CY, DE, DK, CY, DK, CY, DE, DK, CY, D
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### Description

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#### LAMININ 2 AND METHODS FOR ITS USE

5 Cross Reference

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This application claims priority to U.S. Provisional Patent Application Serial Nos. 60/131,720 filed April 30, 1999; 60/139,198 filed June 15, 1999; and 60/143,289 filed July 12, 1999; 60/155,945 filed September 24, 1999; all of which are incorporated herein by reference in their entirety.

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Field of the Invention

This application relates to recombinant laminin 5 and methods for its use.

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**Background of the Invention** 

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Basal laminae (basement membranes) are shect-like, cell-associated extracellular matrices that play a central role in cell growth, tissue development, and tissue maintenance. They are present in virtually all tissues, and appear in the earliest stages of embryonic development.

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Basal laminae are central to a variety of architectural and cell-interactive functions (See for example, Malinda and Kleinman, Int. J. Biochem. Cell Biol. 28:957-959 (1996); Aumailley and Krieg, J. Invest. Dermatology 106:209-214 (1996)). For example:

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1. They serve as architectural supports for tissues, providing adhesive substrata for cells.

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2. They create perm-selective barriers between tissue compartments that impede the migration of cells and passively regulate the exchange of macromolecules. These properties are illustrated by the kidney glomerular basement membrane, which functions as an important filtration structure, creating an effective blood-tissue barrier that is not permeable to most proteins and cells.

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Basal laminae create highly interactive surfaces that can promote cell migration
and cell elongation during embryogenesis and wound repair. Following an injury,
they provide a surface upon which cells regenerate to restore normal tissue
function.

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4. Basal laminae present information encoded in their structure to contacting cells that is important for differentiation and tissue maintenance. This information is communicated to the cells through various receptors that include the integrins, dystroglycan, and cell surface proteoglycans. Signaling is dependent not only on the presence of matrix ligands and corresponding receptors that interact with sufficient affinities, but also on such topographical factors as ligand density in a three-dimensional matrix "landscape", and on the ability of basal lamina components to cluster receptors. Because these matrix proteins can be long-lived, basal laminae create a "surface memory" in the basal lamina for resident and transient cells.

The basal lamina is largely composed of laminin and type IV collagen heterotrimers that in turn become organized into complex polymeric structures. To date, six type IV collagen chains and at least twelve laminin subunits have been identified. These chains possess shared and unique functions and are expressed with specific temporal (developmental) and spatial (tissue-site specific) patterns.

Laminins are a family of heterotrimeric glycoproteins that reside primarily in the basal lamina. They function via binding interactions with neighboring cell receptors, and by forming laminin networks, and they are important signaling molecules that can strongly influence cellular function. Laminins are important in both maintaining cell/tissue phenotype as well as promoting cell growth and differentiation in tissue repair and development.

Laminins are large, multi-domain proteins, with a common structural organization. The laminin molecule integrates various matrix and cell interactive functions into one molecule.

Laminin molecules are comprised of an  $\alpha$ -,  $\beta$ -, and  $\gamma$ -chain subunit joined together through a coiled-coil domain. Within this structure are identifiable domains that possess binding activity towards other laminin and basal lamina molecules, and membrane-bound receptors. Domains VI, IVb, and IVa form globular structures, and domains V, IIIb, and IIIa (which contain cysteine-rich EGF-like elements) form rod-like structures. (Kamiguchi et al., Ann. Rev. Neurosci. 21:97-125 (1998)) Domains I and II of the three chains participate in the formation of a triple-stranded coiled-coil structure (the long arm).

Table 1 shows the individual chains that each laminin type is composed of:

TABLE 1. Known laminin family members

Protein	Chains
Laminin-1	α1β1γ1
Laminin-2	α2β1γ1
Laminin 3	α1β2γ1
Laminin-4	α2β2γ1
Laminin-5	α3β3γ2
Laminin-6	α3β1γ1
Laminin-7	α3β2γ1
Laminin-8	α4β1γ1
Laminin-9	α4β2γ1
Laminin-10	α5β1γ1
Laminin –11	α5β2γ1
Laminin-12	α2β1γ3

Four structurally-defined family groups of laminins have been identified. The first group of five identified laminin molecules all share the  $\beta 1$  and  $\gamma 1$  chains, and vary by their  $\alpha$ -chain composition ( $\alpha 1$  to  $\alpha 5$  chain). The second group of five identified laminin molecules all share the  $\beta 2$  and  $\gamma 1$  chain, and again vary by their  $\alpha$ -chain composition. The third group of identified laminin molecules has one identified member, laminin 5, with a chain composition of  $\alpha 3\beta 3\gamma 2$ . The fourth group of identified laminin molecules has one identified member, laminin 12, with the newly identified  $\gamma 3$  chain ( $\alpha 2\beta 1\gamma 3$ )

Some progress has been made in elucidating the relationship between domain structure and function. (See, for example, Wewer and Engvall, Neuromusc. Disord. 6:409-418 (1996).) The overall sequence similarity among the homologous domains in different chains varies, but it is highest in domain VI (thought to play a key role in laminin polymerization), followed by domains V (possibly involved in protein-protein interactions) and III (entactin/nidogen binding; possible cell adhesion sites), and is lowest in domains I, II (both thought to be involved in intermolecular assembly, and containing possible cell adhesion sites), and G. Not all domains are present in all 3 types of chains. The globular G domain (thought to be involved in cell receptor binding) is present only in the  $\alpha$  chains. Other domains may not be present in all chains within a certain chain type. For example, domain VI is absent from  $\alpha$ 3,  $\alpha$ 4, and  $\gamma$ 2 chains. (Wewer and Engvall, 1996)

As a result of their large size (>600 kD) and unique structure, laminin molecules can be resolved in the electron microscope. (Wewer and Engvall, 1996) Typically, laminins appear as cross-shaped molecules in an electron micrograph. The three short arms of the cross represent the amino terminal portions of each of the three separate laminin chains (one short arm per chain). The long arm of the cross is composed of the C-terminal parts of the three chains, which together form a coiled coil structure. (Wewer and Engvall, 1996) The long arm ends with the globular G domain.

The coiled-coil domain of the long arm is crucial for assembly of the three chains of laminin. (Yurchenco et al., Proc. Natl. Acad. Sci. 94:10189-10194 (1997)). Disulfide bonds bridge and stabilize all three chains in the most proximal region of the long arm and join the  $\beta$  and  $\gamma$  chains in the most distal region of the long arm.

A model of laminin receptor-facilitated self-assembly, based on studies conducted with cultured skeletal myotubes and Schwann cells, predicts that laminins bind to their receptors, which freely diffuse in a fluidic membrane when ligand-free. Receptor engagement forces the laminins into a high local two-dimensional concentration, facilitating their mass-action driven assembly into ordered surface polymers. In this process, the engaged receptors are also reorganized, accompanied by cytoskeletal rearrangements. (Colognato, J. Cell Biol. 145:619-631 (1999)) This reorganization activates the receptors, causing signal transduction with the alteration of cell expression, shape and/or behavior.

One class of laminin receptors are the integrins, which are cell surface receptors that mediate many cell-matrix and cell-cell interactions. Integrins are heterodimers, consisting of an  $\alpha$  and a  $\beta$  subunit. 16  $\alpha$ - and 8  $\beta$ -subunits are known, and at least 22 combinations of  $\alpha$  and  $\beta$  subunits have been identified to date. Some integrins have only one or a few known ligands, whereas others appear to be very promiscuous. Binding to integrins is generally of low affinity, and is dependent on divalent cations. Integrins, activated through binding to their ligands, transduce signals via kinase activation cascades, such as focal adhesion and mitogen-activated kinases. Several different integrins bind different laminin isoforms more or less specifically. (Aumailley et al., In The Laminins, Timpl and Ekblom, eds., Harwood Academic Publishers, Amsterdam. pp. 127-158 (1996))

Laminin 2 is composed of  $\alpha 2$  (400 kD),  $\beta 1$  (approximately 100 kD), and  $\gamma 1$  (approximately 100 kD) chains. The C-terminal G domain of the  $\alpha 2$  chain forms a large globular structure responsible for binding to  $\alpha$ -dystroglycan. (Kamiguchi et al., 1998).

The short arm domains of laminin 1 are involved in the self-aggregation process (Schittney and Yurchenco, J. Cell Biol. 110:825-832 (1990)) and with extracellular matrix components, such as type IV collagen. Homology between the  $\alpha 1$  (laminin 1) and  $\alpha 2$  chains is 58.6%. The significant homology between the  $\alpha 1$  and  $\alpha 2$  chains, especially in the N-terminal domains, and their identical  $\beta$  and  $\gamma$  chains, suggest that laminin 2 has a similar structural organization to laminin 1. (Kamiguchi et al., 1998)

Laminin 2 was originally found in the basement membranes of the placenta, striated muscle, and Schwann cells. (Leivo and Engvall, Proc. Natl. Acad. Sci. USA 85:1544-1548 (1998)) In normal adults, laminin 2 is predominant in the basal lamina of skeletal muscle, where it serves to provide mechanical reinforcement to the sarcolemma by linking the extracellular matrix and the subsarcolemmal cytoskeleton. (Sancs et al., J. Cell Biol. 111:1685-1699 (1990))

Genetic defects affecting the structure or expression of laminin 2 are the causes of a major type of congenital muscular dystrophy (CMD). Laminin 2 has been shown to be specifically required for stabilizing myotubes during skeletal muscle development, and for preventing apoptosis, which is believed to explain some of the pathological events observed in CMD. (Kamiguchi et al., 1998)

In vitro studies have demonstrated that partially purified laminin 2 is important for myotube survival and maintenance of phenotype. (Vachon et al., J. Cell Biol. 134:1483-1497 (1996)) In vivo experiments have shown partial laminin  $\alpha 2$  chain restoration in a laminin  $\alpha 2$  deficient, CMD animal model by primary muscle cell transplantation. (Vilquin et al., J. Cell Biol. 133:185-197)

Laminin 2 is also the predominant laminin isoform present in the endoneurial basement membrane of developing and mature peripheral nerves, and was shown to promote Schwann cell migration, neurite outgrowth, and neurite regeneration (Kamiguchi et al., 1998), as well as myelin formation by oligodendrocytes (Buttery et al., Mol. Cell. Neurosci. 14:199-212 (1999). The results of various experiments have indicated that laminin 2, rather than laminin 1, is important in Schwann cell/basal lamina interactions, especially at early developmental stages. (Kamiguchi et al., 1998) Other

studies have demonstrated that partially purified laminin 2 promotes neuronal cell migration and axon outgrowth (Agius and Cochard, J. Neurosci. 18:328-338 (1998); Kamiguchi et al, 1998; U.S. Patent Nos. 5,444,158; 5,872,231; 5,624,905; and 5,863,743; Bates and Meyer, Develop. Biol. 181:91-101 (1997)). In a laminin 2 deficient CMD animal model, CMD was accompanied by dysmyelination of peripheral motor nerves, indicating that laminin 2 plays an important role in peripheral myelinogenesis.

Partially purified laminin 2 has also been shown to promote cell migration and attachment to a substrate of a variety of cell types, particularly muscle cells and cells of neuronal origin. (U.S. Patent No. 5,444,158; White et al., Am. J. Resp. Biol. 20:787-796 (1999); Engvall et al., Exp. Cell Res. 198:115-123 (1992))

It has also been demonstrated that the molecular basis of the neural tropism of  $Mycobacterium\ leprae$  is attributable to the specific binding of M. leprae to the G domain of the laminin  $\alpha 2$  chain on Schwann cell-axon units, while  $\alpha$ -dystroglycan ( $\alpha DG$ ) was shown to serve as a Schwann cell receptor for M. leprae. (Rambukkana et al., Science 282:2076-2079 (1998); Rambukkana et al., Cell 88:811-821 (1997)). Native  $\alpha DG$  was shown to competitively inhibit the laminin-2 mediated M. leprae binding to primary Schwann cells. (Rambukkana et al. 1998)

Thus, research and therapeutic applications for laminin 2 and fragments thereof include, but are not limited to, peripheral nervous system (PNS) nerve regeneration, treatment of degenerative muscle disorders, regulating angiogenesis, promoting cell attachment and migration, ex vivo cell therapy, improving the biocompatibility of medical devices, improving the "take" of grafts, and preparing improved cell culture devices and media.

At present, there is not a means to isolate adequate substantially purified laminin 2 from cell or tissue sources for research or therapeutic purposes, nor has a means been developed for production of recombinant heterotrimeric laminin 2. Laminin 2 can be partially purified from either placenta, or, in lesser amounts, from skeletal muscle. Human placenta has provided the only source for obtaining up to several milligrams of protein. (Cheng et al., J. Biol. Chem. 272:31525-32, 1997) However preparations of this laminin normally contain about an equal molar quantity of laminin 4 ( $\alpha 2\beta 2\gamma 1$ ) and the protein nidogen (entactin). The nidogen is bound to the laminin through a fairly strong but noncovalent association. It is difficult to remove most of the laminin 4, and even after

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additional steps, a significant contaminating level of laminin 4 remains. Denaturing conditions are required to remove the nidogen.

Therefore, there is a need in the art for adequate amounts of substantially purified laminin-2, and methods for making laminin 2. A preferred method of production is the use of recombinant DNA technology to engineer a cell line of choice to produce recombinant laminin-2. A recombinant-based method of laminin-2 production has several advantages over purification from tissue or isolation from cell lines in culture:

- 1. The recombinantly produced protein is free of pathogens. While this is also true for endogenous cell culture produced protein, protein derived from human tissue carries a risk for contamination by HIV, hepatitis, and other infectious agents.
- 2. Expression levels of the protein, and hence yields, can be improved through the use of genetically engineered genes/vectors that enhance the production of the encoded protein.
- 3. It is possible to engineer additional peptide sequences to the protein chain that provides a binding site for a commercially viable affinity purification procedure.
- 4. The method can provide for the modification of protein structure/function through the addition, substitution, elimination, and/or other modifications of protein domain structures. For example, it may be desirable to introduce an integrin binding site (e.g. RGD), switch integrin recognition sites, or engineer in a stable binding site to a synthetic substrate. Thus, the creation of expression vectors that express laminin chains generates enormous flexibility for future uses and creates a basis for creating second generation "designer" laminins.

#### Summary of the Invention

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The present invention fulfills the need in the art for substantially purified laminin 2 protein, methods for making substantially purified recombinant laminin 2 (hereinafter referred to as r-laminin 2), and methods of using substantially purified laminin 2 for research and therapeutic purposes including, but not limited to, peripheral nerve regeneration, treatment of degenerative muscle disorders, angiogenesis regulation, promoting cell attachment and migration, ex vivo cell therapy, improving the "take" of

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grafts, improving the biocompatibility of medical devices, and preparing improved cell culture devices and media

In one aspect, the present invention provides mammalian cells that have been transfected with expression vector(s) encoding at least one of the laminin  $\alpha 2$ ,  $\beta 1$  and  $\gamma 1$  chains, wherein the cells secrete r-laminin 2.

In another aspect, the present invention provides substantially purified laminin 2 and methods for producing r-laminin 2.

In a further embodiment, the present invention provides a novel, isolated laminin 2  $\alpha$ 2 nucleic acid and  $\alpha$ 2 protein. In this embodiment, the protein product contains an additional 30 amino acids at its carboxyl terminus relative to the previously reported sequence.

In a further aspect, the present invention provides pharmaceutical compositions, comprising substantially purified laminin 2, or the novel recombinant  $\alpha$ 2 protein together with a pharmaceutically acceptable carrier. Such pharmaceutical compositions can optionally be provided with other compounds, such as extracellular matrix components.

The present invention further provides methods for peripheral nerve regeneration, treatment of degenerative muscle disorders, regulating angiogenesis, promoting cell attachment and migration, ex vivo cell therapy, improving the biocompatibility of medical devices, improving the "take" of grafts, and preparing improved cell culture devices and media, comprising providing an amount effective of the substantially purified laminin 2, or pharmaceutical compositions thereof, for the desired outcome.

In a further aspect, the present invention provides improved medical devices or grafts, wherein the improvement comprises applying to the devices or grafts an amount effective of substantially purified laminin 2 or pharmaceutical compositions thereof, for the desired application. Such devices can optionally be provided with other compounds, such as extracellular matrix components to further improve the biocompatibility or the effectiveness of the medical device or graft.

In a further aspect, the invention provides improved cell culture devices, by providing an amount effective of substantially purified laminin 2, or pharmaceutical compositions thereof, for the attachment of cells to a cell culture device for the subsequent proliferation/differentiation/stasis of the cells.

In another aspect, the invention provides a cell culture growth supplement, comprising substantially purified laminin 2. In another aspect, the invention provides an

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improved cell culture growth media, wherein the improvement comprises the addition of substantially purified laminin 2 to the growth medium.

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#### **Brief Description of the Figures**

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Figure 1 is a photograph of an Coomassie blue-stained SDS-polyacrylamide gel of recombinant laminin 2 compared to laminin 1.

Figure 3 is an immunoblot demonstrating the co-polymerization of laminin 2.

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Figure 2 is an electron micrographs of purified recombinant laminin 2.

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Figure 4 is a graph demonstrating C2C12 myoblast adherence to recombinant laminin 2.

Figure 5 shows the correct sequence of the laminin  $\alpha 2$  cDNA and deduced amino acid sequence.

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#### Detailed Description of the Preferred Embodiments

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All references, patents and patent applications are hereby incorporated by reference in their entirety.

Within this application, unless otherwise stated, the techniques utilized may be

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found in any of several well-known references such as: Molecular Cloning: A Laboratory Manual (Sambrook, et al., 1989, Cold Spring Harbor Laboratory Press), Gene Expression Technology (Methods in Enzymology, Vol. 185, edited by D. Goeddel, 1991. Academic Press, San Diego, CA), "Guide to Protein Purification" in Methods in Enzymology (M.P. Deutshcer, ed., (1990) Academic Press, Inc.); PCR Protocols: A Guide to Methods and Applications (Innis, et al. 1990. Academic Press, San Diego, CA), Culture of Animal

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Applications (Innis, et al. 1990. Academic Press, San Diego, CA), Culture of Animal Cells: A Manual of Basic Technique, 2<sup>nd</sup> Ed. (R.I. Freshney. 1987. Liss, Inc. New York, NY), Gene Transfer and Expression Protocols, pp. 109-128, ed. E.J. Murray, The Humana Press Inc., Clifton, N.J.), and the Ambion 1998 Catalog (Ambion, Austin, TX).

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As used herein, "laminin 2" includes both r-laminin 2 and laminin 2 substantially purified from tissue sources.

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As used herein, the term "r-laminin 2" refers to recombinant laminin 2, expressed by a cell that has been transfected with one or more expression vectors comprising at least one nucleic acid sequence encoding a laminin 2 chain selected from the  $\alpha$ 2,  $\beta$ 1 and  $\gamma$ 1 chains, processed forms thereof, or other portions thereof that are capable of forming a

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heterotrimeric laminin 2 and maintaining laminin 2 activity. Such r-laminin 2 can thus comprise α2, β1, and γ1 sequences from a single organism, or from different organisms. Laminin 2 chain DNA sequences and their encoded proteins from a variety of organisms are known in the art. (See, for example, Vuolteenaho ct al., J. Biol. Chem. 265:15611-15616 (1990); Kallunki et al., J. Biol. Chem. 266:221-228 (1991); Pikkarainen et al., J. Biol. Chem. 263:6751-6758 (1988); Sasaki and Yamada, J. Biol. Chem. 262:17111-17117 (1987); Sasaki et al., Proc. Natl. Acad. Sci. 84:935-939 (1987); Pikkarainen et al., J. Biol. Chem. 262:10454-10462 (1987); and Bernier et al., Matrix Biol. 14:447-455 (1995), all references incorporated by reference herein in their entirety).

The invention encompasses those laminin molecules wherein one or two of the chains that make up the recombinant heterotrimeric laminin 2 are encoded by endogenous laminin 2 chains. In a preferred embodiment, r-laminin 2 is produced by cells that are transfected with one or more expression vectors comprising nucleic acid sequences encoding each of mammalian  $\alpha 2$ ,  $\beta 1$  and  $\gamma 1$  chains, processed forms thereof, or other portions thereof that are capable of forming a heterotrimeric laminin 2 and maintaining laminin 2 activity.

In the present invention, laminin 2 is a secreted protein, which is capable of being directed to the ER, secretory vesicles, and the extracellular space as a result of a signal sequence, as well as those proteins released into the extracellular space without necessarily containing a signal sequence. If the secreted protein is released into the extracellular space, the secreted protein can undergo extracellular processing to produce a "mature" protein. Such processing event can be variable, and thus may yield different versions of the final "mature protein". The substantially purified laminin 2 of the present invention includes heterotrimers comprising both the full length and any such processed laminin 2 chains.

As used herein, the term "substantially purified" means that the laminin 2 so designated has been separated from its in vivo cellular environment.

As used herein, a laminin 2 polypeptide chain refers to a polypeptide chain according to one or more of the following:

- (a) comprises a polypeptide structure selected from the group consisting of:
  - 1. R1-R2-R3
  - 2. R1-R2-R3(e)
  - 3. R3

4.

R3(e)

5 5. R1-R3 6. R1-R3(e) 7. R2-R3 10 8. 5 R2-R3(e) wherein R1 is a amino terminal methionine; R2 is a signal sequence that is capable of directing secretion of the polypeptide, wherein the signal sequence may be the natural signal sequence for the particular laminin chain, that of another secreted protein, or 15 an artificial sequence; R3 is a secreted laminin chain selected from a2, \( \beta 1, \) and \( \gamma 1 \) chains; and R3(e) is a secreted laminin chain selected from the  $\alpha$ 2,  $\beta$ 1, and  $\gamma$ 1 chains that further comprises an epitope tag (such as those described below), which can be placed at any 20 position within the laminin chain amino acid sequence; and/or (b) is encoded by a polynucleotide that is substantially similar to on or more of the disclosed laminin chain polynucleotide sequences (SEQ ID NOS.: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31) or fragments thereof; and/or 25 (c) is encoded by a polynucleotide that hybridizes under high or low stringency conditions to coding regions, or portions thereof, of one or more of the recombinant laminin 2 chain DNA sequences disclosed herein (SEQ ID NOS.: 1, 3, 5, 7, 9, 11, 13, 15, 30 17, 19, 21, 23, 25, 27, 29, 31) fragments thereof, or complementary sequences thereof; 20 and/or (d) has at least 70% identity to one or more of the disclosed laminin 2 polypeptide chain amino acid sequences (SEQ ID NOS.: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 35 28, 30, 32, or fragments thereof), preferably at least 80% identity, and most preferably at least about 90% identity. 25 The phrase "substantially similar" is used herein in reference to polynucleotide or polypeptide sequences having one or more conservative variations from the laminin 2 40 sequences disclosed herein, including but not limited to deletions, insertions, inversions, repeats, and substitutions, wherein the resulting laminin chain is functionally equivalent to those disclosed herein. 45 For example, conservative polynucleotide variants may contain alterations in the 30 coding regions, non-coding regions, or both. Especially preferred are polynucleotide variants containing alterations which produce silent substitutions, additions, or deletions, but do not alter the amino acid sequence of the encoded polypeptide. Nucleotide variants 50

produced by silent substitutions due to the degeneracy of the genetic code are preferred. Moreover, variants in which 5-10, 1-5, or 1-2 amino acids are substituted, deleted, or added in any combination are also preferred. Polynucleotide variants can be produced for a variety of reasons, including but not limited to optimizing codon expression for a particular host (change codons in the human mRNA to those preferred by a bacterial host such as *E. coli*).

Naturally occurring conservative variants are called "allelic variants," and refer to one of several alternate forms of a gene occupying a given locus on a chromosome of an organism. (Genes II, Lewin, B., ed., John Wiley & Sons, New York (1985).) These allelic variants can vary at either the polynucleotide and/or polypeptide level. Alternatively, non-naturally occurring conservative variants may be produced by mutagenesis techniques or by direct synthesis.

Using known methods of protein engineering and recombinant DNA technology, conservative polynucleotide variants may be generated to improve or alter the characteristics of the expressed laminin chain polypeptides. For instance, one or more amino acids can be deleted from the N-terminus or C-terminus of the secreted protein. (See, for example, Ron et al., J. Biol. Chem. 268: 2984-2988 (1993); Dobeli et al., J. Biotechnology 7:199-216 (1988)) Ample evidence demonstrates that variants often retain a biological activity similar to that of the naturally occurring protein. (See, for example, Gayleet al., J. Biol. Chem 268:22105-22111 (1993)) Furthermore, even if deleting one or more amino acids from the N-terminus or C-terminus of a polypeptide results in modification or loss of one or more biological functions, other biological activities may still be retained.

Guidance concerning how to make phenotypically silent amino acid substitutions is provided in Bowie, J. U. et al., Science 247:1306-1310 (1990), wherein the authors indicate that there are two main strategies for studying the tolerance of an amino acid sequence to change.

The first strategy exploits the tolerance of amino acid substitutions by natural selection during the process of evolution. By comparing amino acid sequences in different species, conserved amino acids can be identified. These conserved amino acids are likely important for protein function. In contrast, the amino acid positions where substitutions have been tolerated by natural selection indicates that these positions are not critical for protein function. Thus, positions tolerating amino acid substitution could be modified while still maintaining biological activity of the protein.

The second strategy uses genetic engineering to introduce amino acid changes at specific positions of a cloned gene to identify regions critical for protein function. For example, site directed mutagenesis or alanine-scanning mutagenesis (introduction of single alanine mutations at every residue in the molecule) can be used. (Cunningham and Wells, Science 244:1081-1085 (1989).) The resulting mutant molecules can then be tested for biological activity.

As the authors state, these two strategies have revealed that proteins are surprisingly tolerant of amino acid substitutions. The authors further indicate which amino acid changes are likely to be permissive at certain amino acid positions in the protein. For example, most buried (within the tertiary structure of the protein) amino acid residues require nonpolar side chains, whereas few features of surface side chains are generally conserved. Moreover, tolerated conservative amino acid substitutions involve replacement of the aliphatic or hydrophobic amino acids Ala, Val, Leu and Ile; replacement of the hydroxyl residues Ser and Thr; replacement of the acidic residues Asp and Glu; replacement of the amide residues Asn and Gln, replacement of the basic residues Lys, Arg, and His; replacement of the aromatic residues Phe, Tyr, and Trp, and replacement of the small-sized amino acids Ala, Ser, Thr, Met, and Gly.

Besides conservative amino acid substitution, "substantially similar" polypeptides of the present invention include (i) substitutions with one or more of the non-conserved amino acid residues, where the substituted amino acid residues may or may not be one encoded by the genetic code, or (ii) substitution with one or more of amino acid residues having a substituent group, or (iii) fusion of the mature polypeptide with another compound, such as a compound to increase the stability and/or solubility of the polypeptide (for example, polyethylene glycol), or (iv) fusion of the polypeptide with additional amino acids, such as an IgG Fc fusion region peptide, or leader or secretory sequence, or a sequence facilitating purification. Such variant polypeptides are deemed to be "substantially similar" according to the present invention.

For example, polypeptide variants containing amino acid substitutions of charged amino acids with other charged or neutral amino acids may produce proteins with improved characteristics, such as less aggregation. Aggregation of pharmaceutical formulations both reduces activity and increases clearance due to the aggregate's immunogenic activity. (Pinckard et al., Clin. Exp. Immunol. 2:331-340 (1967); Robbins et al., Diabetes 36: 838-845 (1987); Cleland et al., Crit. Rev. Therapeutic Drug Carrier Systems 10:307-377 (1993).)

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"Stringency of hybridization" is used herein to refer to conditions under which nucleic acid hybrids are stable. The invention also includes nucleic acids that hybridize under high stringency conditions (as defined herein) to all or a portion of the coding sequences of the laminin chain polynucleotides disclosed herein, or their complements. The hybridizing portion of the hybridizing nucleic acids is typically at least 50 nucleotides in length. As known to those of skill in the art, the stability of hybrids is reflected in the melting temperature (T<sub>M</sub>) of the hybrids. T<sub>M</sub> decreases approximately 1-1.5°C with every 1% decrease in sequence homology. In general, the stability of a hybrid is a function of sodium ion concentration and temperature. Typically, the hybridization reaction is performed under conditions of lower stringency, followed by washes of varying, but higher, stringency. Reference to hybridization stringency relates to such washing conditions. Thus, as used herein, high stringency refers to an overnight incubation at 42° C in a solution comprising 50% formamide, 5x SSC (750 mM NaCl, 75 mM sodium citrate), 50 mM sodium phosphate (pH 7.6), 5x Denhardt's solution, 10% dextran sulfate, and 20 µg/ml denatured, sheared salmon sperm DNA, followed by washing the filters in 0.1x SSC at about 65°C.

Also contemplated are laminin 2-encoding nucleic acid sequences that hybridize to the polynucleotides of the present invention at lower stringency hybridization conditions. Changes in the stringency of hybridization and signal detection are primarily accomplished through the manipulation of formamide concentration (lower percentages of formamide result in lowered stringency); salt conditions, or temperature. For example, lower stringency conditions include an overnight incubation at 37°C in a solution comprising 6X SSPE (20X SSPE = 3M NaCl; 0.2M NaH<sub>2</sub>PO<sub>4</sub>; 0.02M EDTA, pH 7.4), 0.5% SDS, 30% formamide, 100 ug/ml salmon sperm blocking DNA; followed by washes at 50°C with 1XSSPE, 0.1% SDS. In addition, to achieve even lower stringency, washes performed following stringent hybridization can be done at higher salt concentrations (e.g. 5X SSC).

Note that variations in the above conditions may be accomplished through the inclusion and/or substitution of alternate blocking reagents used to suppress background in hybridization experiments. Typical blocking reagents include Denhardt's reagent, BLOTTO, heparin, denatured salmon sperm DNA, and commercially available proprietary formulations. The inclusion of specific blocking reagents may require modification of the hybridization conditions described above, due to problems with compatibility.

As used herein, "percent identity" of two amino acids or of two nucleic acids is determined using the algorithm of Karlin and Altschul (Proc. Natl. Acad. Sci. USA 87:2264-2268, 1990), modified as in Karlin and Altschul (Proc. Natl. Acad. Sci. USA 90:5873-5877, 1993). Such an algorithm is incorporated into the NBLAST and XBLAST programs of Altschul et al. (J. Mol. Biol. 215:403-410, 1990). BLAST nucleotide searches are performed with the NBLAST program, score = 100, wordlength = 12, to obtain nucleotide sequences homologous to the nucleic acid molecules of the invention. BLAST protein searches are performed with the XBLAST program, score = 50, wordlength = 3, to obtain an amino acid sequence homologus to a polypeptide of the invention. To obtain gapped alignments for comparison purposes, Gapped BLAST is utilized as described in Altschul et al. (Nucleic Acids. Res. 25:3389-3402, 1997). When utilizing BLAST and Gapped BLAST programs, the default paramaters of the respective programs (e.g., XBLAST and NBLAST) are used. See http://www.ncbi.nlm.nih.gov.

Further embodiments of the present invention include polynucleotides encoding laminin 2 chain polypeptides having at least 70% identity, preferably at least 80% identity, and most preferably at least 90% identity to one or more polypeptide sequence contained in SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, or fragments thereof.

As used herein, " $\alpha$ 2 polynucleotide" refers to a polynucleotide encoding an  $\alpha$ 2 laminin chain of the same name. Such polynucleotides can be characterized by one or more of the following: (a) the nucleotides of said polynucleotide may encode an amino acid sequence substantially similar to one or more of the amino acid sequences set forth in SEQ ID NO: 2, 4, 6, 8, 10, 12 or fragments thereof; (b) polynucleotides that encode polypeptides which share at least 70% identity, preferably 80% identity, and most preferably at least 90% identity with one or more of the sequences set forth in SEQ ID NO: 2, 4, 6, 8, 10, 12, or fragments thereof; (c) the  $\alpha$ 2 polynucleotides hybridize under low or high stringency conditions to the coding sequence set forth in one or more of SEQ ID NO: 1, 3, 5, 7, 9, 11, fragments thereof, or complementary sequences thereof; or (d) the  $\alpha$ 2 polynucleotides may encode a polypeptide with a general structure selected from (1) R1-R2-R3; (2) R1-R2-R3(e); (3) R3; (4) R3(e); (5) R1-R3; (6) R1-R3(e); (7) R2-R3; and (8) R2-R3(e); wherein R1 and R2 are as described above, and R3 and R3(e) are as described above but comprise secreted  $\alpha$ 2 chain polypeptides.

As used herein, "β1 polynucleotide" refers to polynucleotides encoding a β1 laminin chain of the same name. Such polynucleotides can be characterized by one or more of the following: (a) the nucleotides of said polynucleotide may encode a polypeptide substantially similar to one or more of the amino acid sequences set forth in SEQ ID NO: 14, 16, 18, 20, or fragments thereof; (b) polynucleotides that encode polypeptides which share at least 70% identity, preferably at least 80%, and most preferably at least 90% identity with one or more of the sequences set forth in SEQ ID NO: 14, 16, 18, 20, or fragments thereof; (c) the β1 cDNAs hybridize under low or high stringency conditions to the coding sequence set forth in one or more of SEQ ID NO: 13, 15, 17, 19, fragments thereof, or complementary sequences thereof; or (d) the β1 polynucleotides may encode a polypeptide with a general structure selected from (1) R1-R2-R3; (2) R1-R2-R3(e); (3) R3; (4) R3(e); (5) R1-R3; (6) R1-R3(e); (7) R2-R3; and (8) R2-R3(c); wherein R1 and R2 are as described above, and R3 and R3(e) are as described above but comprise secreted β1 chain polypeptides.

As used herein, "γ1 polynucleotide" refers to polynucleotides encoding a γ1 laminin chain of the same name. Such polynucleotides can be characterized by one or more of the following: (a) the nucleotides of said polynucleotide may encode an amino acid that is substantially similar to one or more of the sequences set forth in SEQ ID NO: 22, 24, 26, 28, 30, 32, or fragments thereof; (b) polynucleotides that encode polypeptides which share at least 70% identity, preferably at least 80%, and most preferably at least 90% identity with one or more of the sequences set forth in SEQ ID NO: 22, 24, 26, 28, 30, 32, or fragments thereof; (c) the γ1 polynucleotides hybridize under low or high stringency conditions to the coding sequence set forth in one or more of SEQ ID NO: 21, 23, 25, 27, 29, 31, fragments thereof, or complementary sequences thereof; or (d) the γ1 polynucleotides may encode a polypeptide with a general structure selected from (1) R1-R2-R3; (2) R1-R2-R3(e); (3) R3; (4) R3(e); (5) R1-R3; (6) R1-R3(e); (7) R2-R3; and (8) R2-R3(e); wherein R1 and R2 are as described above, and R3 and R3(e) are as described above but comprise secreted γ1 chain polypeptides.

As used herein, the term "epitope tag" refers to a polypeptide sequence that is expressed as part of a chimeric protein, where the epitope tag serves as a recognition site for binding of antibodies generated against the epitope tag, or for binding of other molecules that can be used for affinity purification of sequences containing the tag.

As used herein, the term "increased biocompatibility" refers to reduced induction of acute or chronic inflammatory response, and reduced disruption of the proper differentiation of implant-surrounding tissues for laminin 2-coated biomaterials relative to an analogous, non-coated biomaterial.

In one aspect, the present invention provides r-laminin 2 expressing-cells that have been transfected with an expression vector containing promoter sequences that are operatively linked to nucleic acid sequences encoding at least one polypeptide sequence comprising the  $\alpha 2$ ,  $\beta 1$  and  $\gamma 1$  chains of laminin 2, or fragments thereof, wherein the transfected cells secrete heterotrimeric laminin 2 containing the recombinant laminin chain. In a preferred embodiment, the cells are transfected with recombinant expression vectors containing promoter sequences that are operatively linked to nucleic acid sequences encoding polypeptide sequences comprising each of the mammalian  $\alpha 2$ ,  $\beta 1$  and  $\gamma 1$  chains of laminin 2, or fragments thereof. After the transfection(s), the cells express each of the recombinant laminin 2 chains, which form the heterotrimer, before r-laminin 2 secretion into the media.

In a preferred embodiment, cDNAs encoding  $\alpha 2$ ,  $\beta 1$  and  $\gamma 1$  laminin chains, or fragments thereof, are subcloned into an expression vector. Alternatively, laminin 2  $\alpha 2$ ,  $\beta 1$  and/or  $\gamma 1$  genomic sequences, including one or more introns, can be used.

Any cell capable of expressing and secreting the r-laminin 2 can be used. Preferably, eukaryotic cells are used, and most preferably mammalian cells are used, including but not limited to kidney and epithelial cell lines. In a most preferred embodiment, the mammalian cells do not express all of the laminin 2 chains endogenously. Carbohydrate and disulfide post-translational modifications are believed to be required for laminin 2 protein folding and function. This makes the use of eukaryotic cells preferable for producing functional r-laminin 2, although other systems are useful for obtaining, for example, antigens for antibody production.

"Recombinant expression vector" includes vectors that operatively link a nucleic acid coding region or gene to any promoter capable of effecting expression of the gene product. The promoter sequence used to drive expression of the individual chains or r-laminin 2 may be constitutive (driven by any of a variety of promoters, including but not limited to, CMV, SV40, RSV, actin, EF) or inducible (driven by any of a number of inducible promoters including, but not limited to, tetracycline, ecdysone, steroid-

responsive). The expression vector must be replicable in the host organisms either as an episome or by integration into host chromosomal DNA. In a preferred embodiment, the expression vector comprises a plasmid. However, the invention is intended to include other expression vectors that serve equivalent functions, such as viruses.

In one embodiment, at least one of the laminin chain polynucleotide sequences, or fragments thereof, is operatively linked to a nucleic acid sequence encoding an "epitope tag", so that at least one of the chains is expressed as a fusion protein with an expressed epitope tag. The epitope tag may be expressed as the amino terminus, the carboxy terminus, or internal to any of the polypeptide chains comprising r-laminin 2, so long as the resulting r-laminin 2 remains functional. Any epitope tag may be utilized, so long as it can be used as the basis for affinity purification of the resulting r-laminin 2. Examples of such epitope tags include, but are not limited to FLAG (Sigma Chemical, St. Louis, MO), myc (9E10) (Invitrogen, Carlsbad, CA), 6-His (Invitrogen; Novagen, Madison, WI), and HA (Boehringer Manheim Biochemicals).

In another embodiment, one of the r-laminin 2 chains is expressed as a fusion protein with a first epitope tag, and at least one other r-laminin chain is expressed as a fusion protein with a second epitope tag. This simplifies the purification procedure and facilitates higher recoveries, Alternatively, the same epitope tag can be used to create fusion proteins with more than one of the r-laminin chains.

In a further embodiment, the epitope tag can be engineered to be cleaveable from the r-laminin 2 chain(s). Alternatively, no epitope tag is fused to any of the r-laminin 2 chains, and the r-laminin 2 is purified by standard techniques, including but not limited to affinity chromatography using antibodies against laminin 2 antibodies or other laminin 2 binding molecules.

Transfection of the expression vectors into cukaryotic cells can be accomplished via any technique known in the art, including but not limited to calcium phosphate co-precipitation, electroporation, or liposome mediated-, DEAE dextran mediated-, polycationic mediated-, or viral mediated transfection. Transfection of bacterial cells can be done by standard methods.

In a preferred embodiment, the cells are stably transfected. Methods for stable transfection and selection of appropriate transfected cells are known in the art. In a most preferred embodiment, a CMV promoter driven expression vector is used in a human kidney embryonic 293 cell line.

In one example, media from cells transfected with a single laminin chain are initially analyzed on Western blots using laminin chain-specific antibodies. The expression of single laminin chains following transfection is generally intracellular. Clones showing reactivity against individual transfected chain(s) are verified by any appropriate method, such as PCR, reverse transcription-PCR, or nucleic acid hybridization, to confirm incorporation of the transfected gene. Preferably, analysis of genomic DNA preparations from such clones is done by PCR using laminin chain-specific primer pairs. Media from transfected clones producing all three chains are further analyzed for r-laminin 2 secretion and/or activity, by any appropriate method, including Western blot analysis and cell binding assays. Activity of the r-laminin 2 is preferably analyzed in cell adhesion and protein binding assays.

In another aspect, the present invention provides substantially purified laminin 2, preferably r-laminin 2. In one embodiment, the substantially purified laminin 2 comprises a first chain comprising an  $\alpha 2$  chain polypeptide; a second chain comprising a  $\beta 1$  chain polypeptide; and a third chain comprising a  $\gamma 1$  chain polypeptide. Alternatively, the r-laminin 2 comprises a first chain that is substantially similar to at least one of the sequences shown in SEQ ID NO: 2, 4, 6, 8, 10, 12 or fragments thereof, a second chain that is substantially similar to at least one of the sequence shown in SEQ ID NO: 12, 14, 16, or 18, or fragments thereof; and a third chain that is substantially similar to the sequence shown in SEQ ID NO: 20, 22, 24, or 26, or fragments thereof.

In another embodiment, the substantially purified r-laminin 2 comprises a first chain comprising a polypeptide that is at least about 70% identical to at least one of the sequences shown in SEQ ID NO: 2, 4, 6, 8, or 10, or fragments thereof; a second chain comprising a polypeptide that is at least 70% identical to at least one of the sequences shown in SEQ ID NO: 14, 16, 18, 20, or fragments thereof; and a third chain comprising a polypeptide that is at least 70% identical to at least one of the sequences shown in SEQ ID NO: 22, 24, 26, 28, 30, 32, or fragments thereof, wherein the first, second, and third polypeptides assemble into a recombinant heterotrimeric laminin 2.

It is preferred that at least one of the first, second, or third chains of the substantially purified human r-laminin 2 is expressed as a fusion protein with an epitope tag.

Alternatively, the r-laminin 2 comprises a heterotrimeric polypeptide structure, wherein each individual chain comprises a general structure selected from the group

consisting of: (1) R1-R2-R3; (2) R1-R2-R3(e); (3) R3; (4) R3(e); (5) R1-R3; (6) R1-R3(e); (7) R2-R3; and (8) R2-R3(e)

wherein R1 is a amino terminal methionine; R2 is a signal sequence that is capable of directing secretion of the polypeptide, wherein the signal sequence may be the natural signal sequence for the particular laminin chain, that of another secreted protein, or it may be an artificial sequence; R3 is a secreted  $\alpha 2$ ,  $\beta 1$ , or  $\gamma 1$  laminin chain; and R3(e) is a secreted laminin  $\alpha 2$ ,  $\beta 1$ , and  $\gamma 1$  chain that further comprises an epitope tag (such as those described above), which can be placed at any position within the laminin chain amino acid sequence.

In a preferred embodiment, purification of the r-laminin 2 is accomplished by passing media from the transfected cells through an affinity column. For example, antibodies or other binding molecules that bind to a peptide epitope expressed on at least one of the recombinant chains are attached to an affinity column, and bind r-laminin 2 that has been secreted into the media. The r-laminin 2 is removed from the column by passing excess peptide through the column. The eluted protein can subsequently be further purified, if desired.

Eluted fractions are analyzed by any appropriate method, including gel electrophoresis and Western blot analysis. In a further embodiment, the peptide epitope can be cleaved after purification. In other embodiments, two or three separate r-laminin chains are expressed as fusion proteins, each with a different epitope tag, permitting two or three rounds of purification and a doubly or triply purified r-laminin 2. The epitope tag can be engineered so as to be cleavable from the r-laminin 2 chain(s) after purification. Alternatively, no epitope tag is fused to any of the r-laminin 2 chains, and the r-laminin 2 is purified by standard techniques, including but not limited to affinity chromatography using laminin 2 specific antibodies or other laminin 2 binding molecules.

In another aspect, the present invention provides a novel polynucleotide encoding the laminin  $\alpha 2$  chain, consisting of the sequence shown in SEQ ID NO:1. In another aspect, the present invention provides a novel laminin 2  $\alpha$  polypeptide chain, consisting of the sequence shown in SEQ ID NO:2. These sequences differ from the previously reported sequences, in that the laminin  $\alpha 2$ -chain encoding nucleic acid consists of an extra nucleotide, resulting in the nucleic acid encoding an additional 30 amino acids at the C-terminus over what has previously been reported.

The present invention further provides pharmaceutical compositions comprising

substantially purified laminin 2, and a pharmaceutically acceptable carrier. In a preferred cmbodiment, the pharmaceutical composition comprises substantially purified r-laminin 2. According to this aspect of the invention, other agents can be included in the pharmaceutical compositions, depending on the condition being treated. The pharmaceutical composition may further comprise one or more other compounds, including but not limited to any of the collagens, other laminin types, fibronectin, vitronectin, cadherins, integrins,  $\alpha$ -dystroglycan, entactin/nidogen,  $\alpha$ -dystroglycan, glycoproteins, proteoglycans, heparan sulfate proteoglycan, glycosaminoglycans, epidermal growth factor, vascular endothelial growth factor, fibroblast growth factor, or nerve growth factors, and peptide fragments thereof. In an alternative embodiment, the pharmaceutical compositions comprise the novel laminin  $\alpha$ 2 polypeptide chain of the invention together with a pharmaceutically acceptable carrier.

Pharmaceutical preparations comprising substantially purified laminin 2 can be prepared in any suitable form, and generally comprise the substantially purified laminin 2 in combination with any of the well known pharmaceutically acceptable carriers. The carriers can be injectable carriers, topical carriers, transdermal carriers, and the like. The preparation may advantageously be in a form for topical administration, such as an ointment, gel, cream, spray, dispersion, suspension or paste. The preparations may further advantageously include preservatives, antibacterials, antifungals, antioxidants, osmotic agents, and similar materials in composition and quantity as is conventional. Suitable solutions for use in accordance with the invention are sterile, are not harmful for the proposed application, and may be subjected to conventional pharmaceutical operations such as sterilization and/or may contain conventional adjuvants, such as preservatives, stabilizers, wetting agents, emulsifiers, buffers etc. For assistance in formulating the compositions of the present invention, one may refer to Remington's Pharmaceutical Sciences, 15th Ed., Mack Publishing Co., Easton, Pa. (1975).

In further aspect, the present invention provides methods and kits for peripheral nerve regeneration, treatment of degenerative muscle disorders, regulating angiogenesis, promoting cell attachment and migration, ex vivo cell therapy, improving the biocompatibility of medical devices, improving the "take" of grafts, and preparing improved cell culture devices and media, comprising providing an amount effective of the

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substantially purified laminin 2, or pharmaceutical compositions thereof for the desired outcome. In all of these methods, the use of r-laminin 2 is preferred.

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As used herein, the term "grafts" refers to both natural and prosthetic grafts as well as implants.

The treatment of peripheral nerve injuries is a common surgical problem. Nerve

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injuries can result from trauma, chronic compression, ischemia, radiation, errors of therapy and other causes. The severe forms of injury, in which the nerve is partially or completely disrupted, are difficult or impossible to treat by existing therapies. The basal lamina plays a key role in providing a migration guide for regenerating axons and Schwann cells following such nerve injury. The prognosis for successful regeneration is significantly better if the basement membrane remains intact.

Recently, the feasibility of using basal lamina coated bio-materials as a workable

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grast was demonstrated in a rat model in two studies (Kauppila et al., Exp. Neurol. 123:181-191 (1993); Tong et al., Brain Res. 663:155-162). In the first study, a bovine tendon collagen I grast sheet was impregnated with partially purified, non-recombinant mouse laminin-1, with the cut ends of the rat sciatic nerve (8 mm removed) sutured to the ends of the rolled grast. Function to the affected limb, as judged by electrophysiological and behavioral measurements at 4 months post-operatively, was restored (~60-80% relative to unaffected contralateral nerve) with the laminin grast at a level equivalent to restoring the transected nerve segment. The authors further reported that the laminin grast caused fewer signs of pain. In the second study, the authors created a grast by coating collagen fibrils with purified, non-recombinant laminin and fibronectin, and inserting the modified fibrils in a collagen sleeve. This grast, about 1 cm in length, was again sutured to the proximal and distal end of a transected sciatic nerve. Axonal/Schwann cell growth occurred into the grast with ultimate reattachment with the distal nerve stump. By light

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The studies of Kauppila *et al.* and Tong *et al.* not only demonstrate the value of basal lamina components in regeneration, but also demonstrate therapeutic feasibility. A similar method for enhancing nerve regeneration using a hollow nerve regeneration conduit coated with type I collagen and purified placental laminin (predominately laminin 1) has also been disclosed. (U.S. Patent No. 5,019,087)

and electron microscopy, restoration of essential structural/cellular elements was found in

the graft with ultimate resorption of the graft material. The laminin/fibronectin coat was

essential since the collagen fibrils alone were not sufficient to restore the nerve.

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Thus, in one embodiment, the present invention provides methods to promote peripheral nerve regeneration, comprising coating a nerve graft with an amount effective of substantially purified laminin 2, or pharmaceutical compositions thereof, to promote regeneration of the nerve. Laminin 2 is the predominant laminin isoform present in the endoneurial basement membrane of developing and mature peripheral nerves, and was shown to promote neuronal cell migration and regeneration, axon outgrowth, myelin membrane formation by oligodendrocytes, and Schwann cell migration. (Kamiguchi et al., (1998); Agius and Cochard, J. Neurosci. 18:328-338 (1998); U.S. Patent No. 5,444,158; Buttery et al., Mol. Cell. Neurosci. 14:199-212 (1999); Bates and Meyer, Develop. Biol. 181:91-101 (1997)). The present invention provides a plentiful supply of substantially purified laminin 2, or pharmaceutical compositions thereof, for coating nerve grafts, and thereby promoting neuronal and Schwann cell migration, axonal migration, myelin membrane formation, and nerve regeneration. The graft can comprise a nerve graft, or a prosthetic graft. Both bioresorbable and non-resorbable materials have been used in tubes for bridging nerve gaps. (See for example, Nyilas, et al., (Trans. Soc. Biomater., 6, 85, 1983), Molander, et al. (Biomaterials, Vol. 4, pp. 276-280, October, 1983), Colin, et al., (Journal of Dental Research July, 1984, pp. 987-993).

In another embodiment, r-laminin 2 is used to promote the healing of degenerative muscle disorders. Laminin 2 is known to be important for myotube survival and maintenance of phenotype. (Vachon et al., J. Cell Biol. 134:1483-1497 (1996)). In vitro studies have demonstrated that partially purified laminin 2 promotes myoblast fusion and myotube formation. (Vachon et al., J. Cell Biol. 134:1483-1497 (1996)) In vivo experiments have shown partial laminin  $\alpha$ 2 chain restoration in a laminin  $\alpha$ 2 deficient, CMD animal model by primary muscle cell transplantation. (Vilquin et al., J. Cell Biol. 133:185-197 (1996)) Thus, mammalian cells that express r-laminin 2, or the novel laminin  $\alpha$ 2 chain of the invention, can be used for cell therapy, to treat patients with degenerative muscle disorders such as muscular dystrophies that are characterized by a laminin  $\alpha$ 2 deficiency.

Partially purified laminin 2 has also been shown to promote the migration of and attachment to a substrate of a variety of cell types, particularly muscle cells and cells of neuronal or mesenchymal origin. (U.S. Patent No. 5,444,158; White et al., Am. J. Resp. Biol. 20:787-796 (1999); Engvall et al., Exp. Cell Res. 198:115-123 (1992))

Thus, in another embodiment, substantially purified laminin 2, or pharmaceutical compositions thereof, can be added to medical devices, tissue culture plates, grafts, and cell culture media to provide important ligand substrates to maintain and expand primary explanted human tissue cells. This takes advantage of what has been observed by many investigators over the past decade, i.e., basal lamina components, in particular laminins, provide optimal surfaces for the adhesion, spreading, propagation, and maintenance of the differentiated phenotype of a large variety of cells. This property of substantially purified laminin 2 can be exploited to increase the biocompatibility of a medical device, to permit the maintenance of human cells in a laboratory affording time to find a suitable donor, and for the expansion of cell populations for transplantation and somatic gene therapy. Possible target cells for ex vivo therapy include cells of muscle and neuronal origin, lymphocytes and cells of the immune system, pancreatic islet, parathyroid, adrenal, pituitary, hepatic, cardiac muscle and stem cells.

In another embodiment, the present invention provides methods for regenerating cells and tissues both *in vivo* and *ex vivo*. Many of the current approaches for tissue engineering begin with a collagen/polymer scaffolding that is seeded with appropriate cells that can proliferate and differentiate into cell masses and tissue sub-structures. In the development of these methods, attempts have been made to add coatings to the scaffolding to provide for a more natural surface for cell interactions, with the expectation that cell proliferation and tissue development would be enhanced. Coating these matrices with the substantially purified laminin 2 provides for a natural ligand interactive surface to promote normal cell adherence, cell growth and tissue development. Thus, the availability of substantially purified laminin 2 is expected to significantly improve tissue regeneration procedures.

Laminins, or cell extracts containing laminins, have been shown to regulate angiogenesis in a biphasic manner. (See, for example, Nicosia et al., Dev. Biol. 164:197-206 (1994); Bonfil et al., Int. J. Cancer 58:233-239 (1994)). At lower concentrations (30-300 μg/ml), a laminin-entactin complex stimulated angiogenesis in a three-dimensional culture, while at 3000 μg/ml the same complex was inhibitory to angiogenesis. Thus, in another aspect, the present invention provides methods for regulating angiogenesis, comprising contacting a tissue or culture substrate with an amount effective of laminin 2 or pharmaceutical compositions thereof to regulate angiogenesis. In one embodiment, the laminin 2 is used to promote angiogenesis by contacting a tissue or culture substrate with

an amount effective of laminin 2 to promote angiogenesis. In another embodiment, the laminin 2 is used to inhibit angiogenesis, by contacting the tissue or culture substrate with an amount effective of laminin 2 to inhibit angiogenesis. An example of culture substrates to be contacted with laminin 2 to regulate angiogenesis are those used for tissue engineering purposes.

In a further aspect, the present invention comprises medical devices with improved biocompatibility, wherein the devices are coated with the substantially purified laminin 2, or pharmaceutical compositions thereof, alone or in combination with other proteins or agents that serve to increase the biocompatibility of the device surface. The coated device stimulates cell attachment and provides for diminished inflammation and/or infection at the site of entry of the appliance.

Preferably, the device is made of or coated with a biocompatible metal that may be either stainless steel or titanium. Alternatively, the device is made of or coated with a ceramic material, or a polymer including but not limited to polyester, polyglycolic acid or a polygalactose-polyglycolic acid copolymer.

One particular use of the present invention is to increase neuronal, skeletal muscle, endothelial or mesenchymal cell adhesion to target surfaces. For example, vascular grafts and stents may be coated with substantially purified laminin 2 to stimulate endothelial cell attachment, and to minimize platelet adhesion to the graft or stent surface. Alternatively, bone or connective tissue grafts or prostheses may be coated with substantially purified laminin 2 to stimulate adhesion of the appropriate cell type and improved efficiency of grafting.

If the device is made of a natural or synthetic biodegradable material in the form of a mesh, sheet or fabric, substantially purified laminin 2 may be applied directly to the surface thereof. Appropriate cells may then be cultured on the matrix to form transplantable or implantable devices, including dental abutment pieces, needles, metal pins or rods, indwelling catheters, colostomy tubes, surgical meshes and any other appliance for which coating with the substantially purified laminin 2 is desirable. Alternatively, the devices may be implanted and cells may be permitted to attach in vivo.

Coupling of the substantially purified laminin 2 may be non-covalent (such as by adsorption), or by covalent means. The device may be immersed in, incubated in, or sprayed with substantially purified laminin 2 or pharmaceutical compositions thereof.

The dosage regimen for various treatments using the substantially purified laminin

2 of the present invention is based on a variety of factors, including the type of injury or condition, the age, weight, sex, medical condition of the individual, the severity of the condition, and the route of administration. Thus, the dosage regimen may vary widely, but can be determined routinely by a physician using standard methods. Laminins are extremely potent molecules, and one or a few molecules per cell could produce an effect. Thus, effective doses in the pico-gram per milliliter range are possible if the delivery is optimized. Laminins are sometimes present in an insoluble form in the basement membrane and have the capability of polymerizing at concentrations as low as about 50 µg/ml, depending on the laminin isoform and the conditions. Laminins can also polymerize into a gel at a concentration of 2-3 mg/ml. Dosage levels of the order of between 1 ng/ml and 10 mg/ml are thus useful for all methods disclosed herein, preferably between about 1 µg/ml and about 3 mg/ml.

The present invention also provides a method for inducing cell attachment to the device (as disclosed above), comprising coating the appliance with substantially purified laminin 2 prior to incubation with cells appropriate for the desired application.

In another aspect of the present invention, substantially purified laminin 2 is used for the culture of cells, including but not limited to neuronal, skeletal muscle, fibroblasts, Schwann cells, cells of mesenchymal origin, and endothelial cells, by contacting the cells with an amount effective of substantially purified laminin 2 to stimulate attachment and proliferation/differentiation/stasis of cells. The substantially purified laminin 2 can either be provided in the cell culture medium, or as a cell culture medium supplement, or may be coated on the surface of a cell growth substrate. In a preferred embodiment, the method further includes contacting the cells with other compounds, including but not limited to any of the collagens, other laminin types, fibronectin, vitronectin, cadherins, entactin/nidogen,  $\alpha$ -dystroglycan, glycoproteins, proteoglycans, heparan sulfate proteoglycan, glycosaminoglycans, epidermal growth factor or nerve growth factors, and peptide fragments thereof.

The cells may comprise primary cells or cell culture cell lines. The methods of this aspect of the invention can be used in vivo, ex vivo, or in vitro.

In a preferred embodiment, r-laminin 2 is used to coat the surface of a substrate, to promote cell adhesion to the substrate, and to stimulate cell proliferation/differentiation/stasis. The substrate used herein may be any desired substrate. For laboratory use, the substrate may be as simple as glass or plastic. For use in

vivo, the substrate may be any biologically compatible material capable of supporting cell growth. Suitable substrate materials include shaped articles made of or coated with such materials as collagen, regenerated collagen, polyglycolic acid, polygalactose, polylactic acid or derivatives thereof; biocompatible metals such as titanium and stainless steel; ceramic materials including prosthetic material such as hydroxylapatite; synthetic polymers including polyesters and nylons; polystyrene; polyacrylates; polytetrafluoroethylene and virtually any other material to which biological molecules can readily adhere.

In a further aspect, the present invention provides cell growth substrates for the adhesion and proliferation of cells in culture, by providing an amount effective of substantially purified laminin 2 for the attachment of cells to a cell culture device for the attachment and subsequent proliferation, differentiation, or stasis of the cells. The substrates may comprise any of the substrates discussed above. Preferably, r-laminin 2 is coated on the surface of the substrate at a concentration of between about 1 ng/ml and about 10 mg/ml, and more preferably 1 ng/ml and about 10 µg/ml.

In another aspect of the present invention, an improved cell culture medium is provided, wherein the improvement comprises addition to the cell culture medium of an effective amount of substantially purified laminin 2 to the cell culture medium to promote the adherence, proliferation, differentiation, or stasis of cells. Any cell culture media that can support the growth of cells can be used with the present invention. Such cell culture media include, but are not limited to Basal Media Eagle, Dulbecco's Modified Eagle Medium, Iscove's Modified Dulbecco's Medium, McCoy's Medium, Minimum Essential Medium, F-10 Nutrient Mixtures, Opti-MEM® Reduced-Serum Medium, RPMI Medium, and Macrophage-SFM Medium or combinations thereof.

The improved cell culture medium can be supplied in either a concentrated (ie: 10X) or non-concentrated form, and may be supplied as either a liquid, a powder, or a lyophilizate. The cell culture may be either chemically defined, or may contain a serum supplement. Culture media is commercially available from many sources, such as GIBCO BRL (Gaithersburg, MD) and Sigma (St. Louis, MO). In an alternative embodiment, the r-laminin 2 is used as a cell culture supplement.

The present invention may be better understood with reference to the accompanying examples that are intended for purposes of illustration only and should not be construed to limit the scope of the invention, as defined by the claims appended hereto.

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#### Examples

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Recombinant Laminin-2

cDNAs coding for the complete open reading frame of the human \$1 chain and the human yl chain have been described. (Kallunki et al., J. Biol. Chem. 266:221-228 (1991); Pikkarainen et al., J. Biol. Chem. 262:10454-10462 (1987); Pikkarainen et al., J. Biol. Chem. 263:6751-6758 (1988); Pikkarainen et al., Eur. J. Biochem. 209:571-582 (1992)). The yl cDNA was modified to contain a 3' end (corresponding to the C-terminal end) insertion coding for the FLAG peptide epitope tag (SEQ ID NO:25). The complete human laminin a2 cDNA was constructed from the large (approximately 2/3 of open reading frame) cDNA as described in (Vuolteenaho et al., J. Cell Biol. 124:381-394 (1994)) with the C-terminal (3'-end) cDNA as described in (Ehrig et al., Proc. Natl. Acad. Sci. The  $\beta$ 1,  $\gamma$ 1, and  $\alpha$ 2 cDNAs were inserted into the pCIS 87:3264-3268 (1990)). (Genentech, South San Francisco, CA), pRC-CMV, and pCEP4 (InVitrogen, Inc., Carlsbad, CA) mammalian expression vectors respectively. pRC-CMV contained a neo (G418) expression cassette and pCEP4 contained a puromycin expression cassette, each under a separate promoter. Transfection of human embryonic kidney 293 cells (adenovirus transformed, ATCC CRL 1573) with the  $\gamma$ 1-FLAG expression vector was carried out by calcium phosphate precipitation in 35 mm plastic dishes as previously described (Yurchenco et al., Proc. Natl. Acad. Sci. 94:10189-94 (1997)). Laminin y1 expressing stable clones were selected in the presence of G418 antibiotic. These cells were found to express the laminin yl chain that reacted with both laminin and FLAGspecific antibodies in immunoblots. One such clone was subsequently co-transfected with the expression vector DNA coding for the a2 and \$1 laminin chains. New clones were selected in the presence of G418+ puromycin. A clone (designated #44) was determined to express all three laminin 2 chains, by using polyclonal antibodies specific for placental laminin and the α2-G domain, β1 chain, and FLAG epitope tag (Cheng et al., J. Biol.

Purification of recombinant laminin 2

pooled for purification of secreted protein.

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Chem. 272:31525-32 (1997); Rambukkana et al., Cell 88:811-821 (1997)). This clone was expanded in tissue culture. Conditioned serum-containing medium was collected and

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30 Functional Data

electron microscopy (Figure 2).

Recombinant laminin 2 was found to possess self-assembly activity in a copolymerization assay (Figure 3). A fixed trace amount of r-laminin 2 was mixed with increasing concentrations of laminin 1 in separate tubes (each containing a small amount

The procedure is described for 100 ml of pooled conditioned medium. Purification was carried out at 4°-10°C in a cold room. A small column was packed with two ml of heparin-Sepharose-4B beads and equilibrated with Tris-buffer (50 mM Tris-HCl, pH 7.4, containing 1 MM EDTA and 0.1 mM PMSF) diluted 2:1 with water. The medium was passed through the column. The column was then washed with several volumes of Trisbuffer to decrease the NaCl concentration. One ml of anti-FLAG M2 agarose affinity gel suspension (Sigma-Aldrich, St. Louis, MO) was added to the preparation and used to absorb the recombinant protein bearing the FLAG epitope tag. After washing five times with Tris-buffer, 0.1 mg (in one ml) of FLAG peptides (Sigma-Aldrich) was added to elute the recombinant laminin protein from the beads. The protein was freed of peptides

with a spin column. Recombinant protein was characterized by SDS-polyacrylamide gel

electrophoresis (SDS-PAGE) (Figure 1), immunoblotting, and Pt/C rotary shadow

Recovered yields of recombinant laminin 2 were 6  $\mu$ g/ml purified protein from conditioned medium (determined from a 100 ml batch preparation). The recombinant laminin had three Coomassie blue-staining bands, the larger corresponding to the  $\alpha 2$  subunit. (Figure 1) Some unprocessed (i.e.: uncleaved)  $\alpha 2$  chain was typically observed. The cleaved version contained a high molecular weight band (approximately 300 kDa) and a 75 kDa band, the latter the predicted G fragment. (Cheng et al., J. Biol. Chem. 272:31525-32 (1997) The two forms of laminin 2 could be separated from each other by heparin affinity chromatography.

Figure 2 is an electron micrograph of purified r-laminin 2, which was dialyzed into 0.15M ammonium bicarbonate, mixed with glycerol to a final ratio of 6:4 glycerol:buffer, and nebulized onto freshly cleraved mica. The sample was evacuated in a Balzars BAF-500K freeze-etch unit and rotary shadowed at an 8° angle with 0.9 nm Pt/C as described (Yurchenco et al., Proc. Natl. Acad. Sci. 94:10189-94 (1997)). As can be seen from the figure, r-laminin 2 demonstrates the cruciform structure that is typical of endogenously expressed laminin molecules.

of bovine serum albumin (BSA)) and incubated at  $37\mu\text{C}$  as described (Cheng et al., J. Biol. Chem. 272:31525-32 (1997)). The incubation mixtures were then centrifuged in supernatant (S) and polymer pellet (P) fractions. Laminin 2 was detected with FLAG-specific antibody. At higher conentrations, increasing fractions of laminin 2 are detected in the pellet fraction, evidence for laminin-type polymerization.

R-laminin 2 was also found to support adhesion and spreading of C2C12 myoblasts (**Figure 4**), but not HT1080 fibrosarcoma cells (data not shown). Cultured myoblasts were added to 96-well culture dishes previously coated with two preparations of r-laminin 2 (two left bars), or with r-laminin 2 bearing different deletions of the G domain, all at 5  $\mu$ g/ml. Deletion of G1-3 sub-domains (which bears the  $\alpha$ 7 $\beta$ 1 integrin binding site), or all of G (which also removes the dystroglycan sites) greatly reduced binding.

#### Human laminin 0.2 polynucleotide and polypeptide

We have determined that the published sequence of the human laminin  $\alpha 2$  nucleic acid and protein sequences (Ehrig et al., PNAS 87:3264-3268 (1990) are incorrect. An erroneous dropped G base that should lie near the 3' end of the nucleic acid sequence (Figure 5), leads to a prediction of a prematurely truncated laminin alpha2-G domain. The correct amino acid sequence for the  $\alpha 2$  chain protein is shown in Figure 5.

One of the most serious consequences of the erroneous sequence may be that the end of the G domain is predicted to lack a cysteine residue that is conserved in different laminins, and is present in the corrected sequence presented here. It is thought that this cysteine pairs with another cysteine in the G domain and is important for protein conformation. Furthermore, if the incorrect sequence is used, an epitope tag placed at the apparent C-terminus will in fact be out of frame, and thus the epitope tag will not be functional.

The present invention is not limited by the aforementioned particular preferred embodiments. It will occur to those ordinarily skilled in the art that various modifications may be made to the disclosed preferred embodiments without diverting from the concept of the invention. All such modifications are intended to be within the scope of the present invention.

### Claims

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5		We cla	aim	
		1.	Substantially purified laminin 2.	
10	5	2.	The substantially purified laminin 2 of claim 1, comprising rec	combinant laminin 2.
		3.	The substantially purified recombinant laminin 2 of claim 2 co	omprising:
15			a first chain comprising a polypeptide that is substantially sim	ilar to an α2 laminin
13		chain;		
	10		a second chain comprising a polypeptide that is substantially s	imilar to a β1
		lamini	n chain; and	
20			a third chain comprising a polypeptide that is substantially sim	nilar to a y1 laminin
		chain;		
			wherein the first, second, and third chains are assembled into	recombinant
25	15	hetero	trimeric laminin 2.	
		4.	The substantially purified recombinant laminin 2 of claim 2 co	omprising:
			a first chain encoded by a polynucleotide that hybridizes under	r high stringency
30		condit	ions to a coding region of one or more of SEQ ID NO:1, 3, 5, 7	1, 9, 11, or fragments
	20	thereo	f;	
			a second chain encoded by a polynucleotide that hybridizes up	nder high stringency
0.5		condit	ions to a coding region of one or more of SEQ ID NO:13, 15, 1	7, 19 or fragments
35		thereo	f; and	
			a third chain encoded by a polynucleotide that hybridizes und	er high stringency
	25	condit	ions to a coding region of one or more of SEQ ID NO: 21, 23,	25, 27, 29, 31 or
40		fragme	ents thereof;	
			wherein the first, second, and third chains are assembled into	recombinant
		hetero	trimeric laminin 2.	

5. The substantially purified recombinant laminin 2 of claim 2 comprising:
a first chain comprising a polypeptide at least 70% identical to one or more of SEQ
ID NO:2, 4, 6, 8, 10, 12 or fragments thereof;

a second chain comprising a polypeptide at least 70% identical to one or more of 31

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SEQ ID NO:14, 16, 18, 20 or fragments thereof; and 5 a third chain comprising a polypeptide at least 70% identical to one or more of SEQ ID NO:22, 24, 26, 28, 30, 32, or fragments thereof; wherein the first, second, and third chains are assembled into recombinant 10 heterotrimeric laminin 2. The substantially purified recombinant laminin 2 of claim 2 comprising a first, second, and third polypeptide chain, wherein the first, second, and third polypeptide 15 chains each comprise a general structure selected from the group consisting of: (1) R1-R2-R3; (2) R1-R2-R3(e); (3) R3; (4) R3(e); (5) R1-R3; (6) R1-R3(e); (7) R2-R3; and (8) R2-R3(e) 20 wherein R1 is a amino terminal methionine; R2 is a signal sequence that is capable of directing secretion of the polypeptide, wherein the signal sequence may be the natural signal sequence for the particular laminin chain, that of another secreted protein, or it may be an artificial sequence; R3 is a secreted \( \alpha 2 \) laminin chain for the first polypeptide chain, 25 a secreted \$1 laminin chain for the second polypeptide chain, and y1 laminin chain for the third polypeptide chain; and R3(e) is identical to R3, but further comprises an epitope tag. 30 7. Recombinant laminin 2-expressing host cells. 20 8. The recombinant laminin 2-expressing host cells of claim 7, wherein the cells express recombinant laminin 2 comprising: 35 a first chain comprising a recombinant polypeptide that is substantially similar an laminin a2 polypeptide; 25 a second chain comprising a recombinant polypeptide that is substantially similar to a laminin \$1 polypeptide sequence; and 40 a third chain comprising a recombinant polypeptide that is substantially similar to a laminin yl polypeptide sequence; wherein the cell expresses the first, second, and third chains, and wherein the first, 45

media by the cultured cell.

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second, and third chains assemble into recombinant laminin 2 that is secreted into the

9. The recombinant laminin 2-expressing host cells of claim 7, wherein the cells 5 express recombinant laminin 2 comprising: a first chain encoded by a polypeptide that hybridizes under high stringency conditions to a coding region of one or more of SEQ ID NO:1, 3, 5, 7, 9, 11, or fragments 10 5 thereof; a second chain encoded by a polypeptide that hybridizes under high stringency conditions to a coding region of one or more of SEQ ID NO:1, 15, 17, 19, or fragments thereof; and 15 a third chain encoded by a polypeptide that hybridizes under high stringency conditions to a coding region of one or more of SEQ ID NO: 21, 23, 25, 27, 29, 31, or 10 fragments thereof; 20 wherein the cell expresses the first, second, and third chains, and wherein the first, second, and third chains assemble into recombinant laminin 2 that is secreted into the media by the cultured cell. 15 25 10. The recombinant laminin 2-expressing host cells of claim 7, wherein the cells express recombinant laminin 2 comprising: a first chain comprising a polypeptide at least 70% identical to one or more of SEQ ID NO:2, 4, 6, 8, 10, 12, or fragments thereof; 30 20 a second chain comprising a polypeptide at least 70% identical to one or more of SEO ID NO:14, 16, 18, 20, or fragments thereof; and a third chain comprising a recombinant polypeptide at least 70% identical to one or 35 more of SEQ ID NO:22, 24, 26, 28, 30, 32, or fragments thereof; wherein the cell expresses the first, second, and third chains, and wherein the first, 25 second, and third chains assemble into recombinant laminin 2 that is secreted into the media by the cultured cell. 40 The recombinant laminin 2-expressing host cells of claim 7, wherein the cells express recombinant laminin 2 comprising a first, second, and third polypeptide chain, 45 wherein the first, second, and third polypeptide chains each comprise a general structure selected from the group consisting of: (1) R1-R2-R3; (2) R1-R2-R3(e); (3) R3; (4) R3(e); (5) R1-R3; (6) R1-R3(e); (7) R2-R3; and (8) R2-R3(e) 50

5		of directing s	ein R1 is a amino terminal methionine; R2 is a signal sequence that is capable secretion of the polypeptide, wherein the signal sequence may be the natural nee for the particular laminin chain, that of another secreted protein, or it may
10	5	a secreted β1	al sequence; R3 is a secreted $\alpha 2$ laminin chain for the first polypeptide chain, laminin chain for the second polypeptide chain, and $\gamma 1$ laminin chain for the otide chain; and R3(e) is identical to R3, but further comprises an epitope tag.
15		12. The h	nost cells of any of claims 7-11, wherein the host cell is a mammalian cell.
20	10		nost cells of claim 12, wherein at least one of the first, second, or third chains as a fusion protein with an epitope tag.
			thod of purifying recombinant laminin 2, comprising:  providing the host cells of claim 12;
25	15	b. expression o	growing the cells in cell culture medium under conditions to stimulate f the recombinant laminin 2 chains;
30	20	c. column, whe	passing the cell culture medium through an affinity chromatography rein the column contains a compound that binds to the recombinant laminin
35		đ.	washing the affinity column to remove unbound materials; and
40	25	e.	eluting the bound recombinant laminin 2 from the column.
		15. Subst	tantially purified recombinant laminin 2 isolated according to the method of
45	30	16. A ph	armaceutical composition comprising: laminin 2; and a pharmaceutically acceptable carrier.
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The pharmaceutical composition of claim 16, wherein the laminin 2 comprises

recombinant laminin 2. 10 18. A method to promote nerve regeneration in a mammal, comprising administering to a mammal in need thereof an amount effective of the laminin 2 of any of claims 1-5 and 15 to promote nerve regeneration. 15 A method for regulating angiogenesis, comprising contacting a tissue in need 19. thereof with an amount effective to regulate angiogenesis of the laminin 2 of any of claims 10 1-5 and 15 to regulate angiogenesis. 20 20. A method to improve the biocompatibility of a medical device, comprising contacting the medical device with an amount effective of the laminin 2 of any of claims 1-5 and 15 to improve the biocompatibility of the medical device. 25 21. An improved medical device, comprising a medical device with an amount effective of the laminin 2 of any of claims 1-5 and 15 to improve the biocompatibility of the medical device. 30 20 A method to promote cell adhesion to a surface, comprising contacting cells with an amount effective of the laminin 2 of any of claims 1-5 and 15 to promote cell adhesion 35 to a surface. 23. An improved cell growth surface, wherein the improvement consists of providing a cell growth surface that has been coated with an amount effective of the laminin 2 of any of claims 1-5 and 15 to promote cell attachment to the cell growth surface. 40 A method to promote nerve regeneration in a mammal, comprising administering to a mammal in need thereof an amount effective of the pharmaceutical composition of 45 claim16 or 17 to promote nerve regeneration. 50

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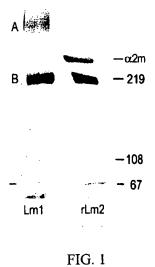
WO 00/66730	PCT/US00/113

25. A method for regulating angiogenesis, comprising contacting a tissue in need 5 thereof with an amount effective to regulate angiogenesis of the pharmaceutical composition of claim 16 or 17 to regulate angiogenesis. 10 26. A method to improve the biocompatibility of a medical device, comprising contacting the medical device with an amount effective of the pharmaceutical composition of claim 16 or 17 to improve the biocompatibility of the medical device. 15 27. An improved medical device, comprising a medical device with an amount effective of the pharmaceutical composition of claim 16 or 17 to improve the biocompatibility of the medical device. 20 28. A method to promote cell adhesion to a surface, comprising contacting cells with an amount effective of the pharmaceutical composition of claim 16 or 17 to promote cell adhesion to a surface. 25 An improved cell growth surface, wherein the improvement consists of providing a cell growth surface that has been coated with an amount effective of the pharmaceutical composition of claim 16 or 17 to promote cell attachment to the cell growth surface. 30 30. An isolated recombinant laminin a2 chain polynucleotide consisting essentially of 20 the sequence shown in SEQ ID NO:1. A substantially purified laminin a2 chain polypeptide consisting essentially of the 35 sequence shown in SEQ ID NO:2. 25 32. An expression vector comprising the polynucleotide of SEQ ID NO:1. 40 33. A host cell transfected with the expression vector of claim 32. 34. A method for treating degenerative muscle disorders in a mammal, comprising 45 administering the host cells of any of claims 7-13 and 33 to a mammal in need thereof,

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wherein the host cells secrete an amount effective of the recombinant laminin 2 or the recombinant laminin  $\alpha$ 2 chain polypeptide, to treat the degenerative muscle disorder.

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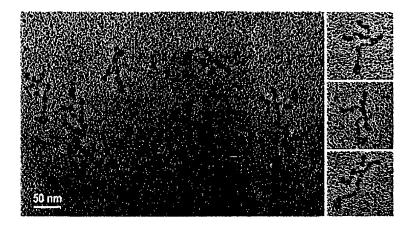


FIG. 2

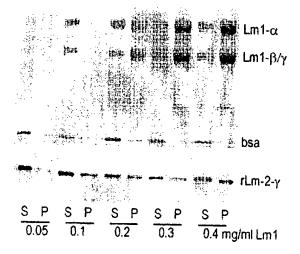


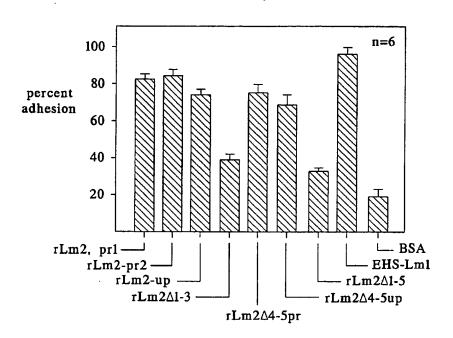
FIG.3

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## FIG. 4

C2C12 myoblasts



Substrate (5 µg/ml)

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							5	/5	
	51	L P R	TTGCCAAGGC	AACGGTTCCG	11		.د	, <i>3</i>	
	41	R L I	GAGGTTAATT	TTTCCGTGTC GTTCGGTGAC CTCCAATTAA AACGGTTCCG	ᆏ				
$\overline{FIG.5}$	31	A S H W	CAAGCCACTG	GTTCGGTGAC	91			Site of missing	base-pair
FI	21	K G T A S H	AAAGGCACAG		81			SOF	Д
	12	K L T	TCAGATCCCT GAAGCTCACC AAAGGCACAG CAAGCCACTG GAGGTTAATT	AGTCTAGGGA CTTCGAGTGG	71		A	E	
		R S L	TCAGATCCCT	AGTCTAGGGA		N W	CCTGGAACTG	GGACCTTGAC T	
	5,	+3	-	4	5,	+3	5	10	

SUBSTITUTE SHEET (RULE 26)

## SEQUENCE LISTING

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		att Ile														634
		atc Ile														682
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		cca Pro 230														778
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		gac Asp														874
		gtc Val														922
		agg Arg														970
		gag Glu 310														1018
		cat His														1066
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					tca Ser											1642
					ata Ile											1690
					cga Arg											1738
cct Pro	cag Gln 565	cag Gln	atc Ile	agc Ser	atc Ile	agt Ser 570	aac Asn	gcg Ala	gag Glu	gcc Ala	cgg Arg 575	caa Gln	gcc Ala	ctg Leu	ccg Pro	1786
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gct gtc tcc tat cct Ala Val Ser Tyr Pro 710			
tgt cag tgc cca cca Cys Gln Cys Pro Pro 725			
cct agg cac agg cga Pro Arg His Arg Arg 740			
cca tgt cag tgc ttt Pro Cys Gln Cys Phe 760	Gly His Ala		
gaa tgc ctg aac tgt Glu Cys Leu Asn Cys 775			
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tgt caa ccc tgt gcc Cys Gln Pro Cys Ala 805			
cca acg tgc cat tta Pro Thr Cys His Leu 820			
cct gtc ggg tac aca Pro Val Gly Tyr Thr 840	Gly Pro Arg		

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		Cys					Leu					qaA		aag Lys		3130
	Arg					Pro					Glu			tct Ser		3178
Суз	gca Ala 1045	ccc Pro	aat Asn	acc Thr	Trp	ggc Gly 050	cac His	agc Ser	att Ile	Thr	act Thr 055	ggt Gly	tgt Cys	aag Lys	gct Ala	3226
	Asn			Thr					qaA					gta Val 1		3274
			Сув					Lys					Lys	tgt Cys .090		3322

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His Met Asp Leu Met Arg Glu Asp Leu His Leu Glu Pro Phe Tyr Trp	3754 3802
His Met Asp Leu Met Arg Glu Asp Leu His Leu Glu Pro Phe Tyr Trp 1220 1225 1230 1235  aaa ctt cca gaa caa ttt gaa gga aag aag ttg atg gcc tat ggg ggc Lys Leu Pro Glu Gln Phe Glu Gly Lys Lys Leu Met Ala Tyr Gly Gly	
His Met Asp Leu Met Arg Glu Asp Leu His Leu Glu Pro Phe Tyr Trp 1220 1225 1230 1235  aaa ctt cca gaa caa ttt gaa gga aag aag ttg atg gcc tat ggg ggc Lys Leu Pro Glu Gln Phe Glu Gly Lys Lys Leu Met Ala Tyr Gly Gly 1240 1245 1250  aaa ctc aag tat gca atc tat ttc gag gct cgg gaa gaa aca ggt ttc Lys Leu Lys Tyr Ala Ile Tyr Phe Glu Ala Arg Glu Glu Thr Gly Phe	3802
His Met Asp Leu Met Arg Glu Asp Leu His Leu Glu Pro Phe Tyr Trp 1220 1225 1230 1235  aaa ctt cca gaa caa ttt gaa gga aag aag ttg atg gcc tat ggg ggc Lys Leu Pro Glu Gln Phe Glu Gly Lys Lys Leu Met Ala Tyr Gly Gly 1240 1245 1250  aaa ctc aag tat gca atc tat ttc gag gct cgg gaa gaa aca ggt ttc Lys Leu Lys Tyr Ala Ile Tyr Phe Glu Ala Arg Glu Glu Thr Gly Phe 1255 1260 1265  tct aca tat aat cct caa gtg atc att cga ggt ggg aca cct act cat Ser Thr Tyr Asn Pro Gln Val Ile Ile Arg Gly Gly Thr Pro Thr His	3802 3850
His Met Asp Leu Met Arg Glu Asp Leu His Leu Glu Pro Phe Tyr Trp 1220 1225 1230 1235  aaa ctt cca gaa caa ttt gaa gga aag aag ttg atg gcc tat ggg ggc Lys Leu Pro Glu Gln Phe Glu Gly Lys Lys Leu Met Ala Tyr Gly Gly 1240 1245 1250  aaa ctc aag tat gca atc tat ttc gag gct cgg gaa gaa aca ggt ttc Lys Leu Lys Tyr Ala Ile Tyr Phe Glu Ala Arg Glu Glu Thr Gly Phe 1255 1260 1265  tct aca tat aat cct caa gtg atc att cga ggt ggg aca cct act cat Ser Thr Tyr Asn Pro Gln Val Ile Ile Arg Gly Gly Thr Pro Thr His 1270 1275 1280  gct aga att atc gtc agg cat atg gct cct ctt att ggc caa ttg Ala Arg Ile Ile Val Arg His Met Ala Ala Pro Leu Ile Gly Gln Leu	3850 3850
His Met Asp Leu Met Arg Glu Asp Leu His Leu Glu Pro Phe Tyr Trp 1220 1225 1230 1235  aaa ctt cca gaa caa ttt gaa gga aag aag ttg atg gcc tat ggg ggc Lys Leu Pro Glu Gln Phe Glu Gly Lys Lys Leu Met Ala Tyr Gly Gly 1240 1245 1250  aaa ctc aag tat gca atc tat ttc gag gct cgg gaa gaa aca ggt ttc Lys Leu Lys Tyr Ala Ile Tyr Phe Glu Ala Arg Glu Glu Thr Gly Phe 1255 1260 1265  tct aca tat aat cct caa gtg atc att cga ggt ggg aca cct act cat Ser Thr Tyr Asn Pro Gln Val Ile Ile Arg Gly Gly Thr Pro Thr His 1270 1275 1280  gct aga att atc gtc agg cat atg gct gct cct ctg att ggc caa ttg Ala Arg Ile Ile Val Arg His Met Ala Ala Pro Leu Ile Gly Gln Leu 1285 1290 1295  aca agg cat gaa att gaa atg aca gag aaa gaa tgg aaa tat tat ggg Thr Arg His Glu Ile Glu Met Thr Glu Lys Glu Trp Lys Tyr Tyr Gly	3802 3850 3898

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Gln	gga Gly L365	cgt Arg	gga Gly	aca Thr	Thr	atg Met 1370	act Thr	cct Pro	cca Pro	Ala	gac Asp 1375	ttg Leu	att Ile	gaa Glu	aaa Lys	4186
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Сув					Cys	gat Asp 1530				Ser						4666
	Pro			Gly		tgc Cys			Arg					Gly		4714
			Gly			cac His		His					Trp			4762
						tgc Сув										4810

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				ctg Leu												7738

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8410

8458

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	Phe	gcc Ala 950				Gly					Gly					8938
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gtc Val	Thr	gcc Ala 030	aac Asn	aag Lys	atc Ile	Lys	cac His 035	cgc Arg	att Ile	gag Glu	Leu	aca Thr 040	gtc Val	gat Asp	gly ggg	9178

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Ala His Gln Gln Arg Gly Leu Phe Pro Ala Val Leu Asn Leu Ala Ser 35 40 45												
Asn Ala Leu Ile Thr Thr Asn Ala Thr Cys Gly Glu Lys Gly Pro Glu 50 55 60												
Met Tyr Cys Lys Leu Val Glu His Val Pro Gly Gln Pro Val Arg Asn 65 70 75 80												
Pro Gln Cys Arg Ile Cys Asn Gln Asn Ser Ser Asn Pro Asn Gln Arg 85 90 95												
His Pro Ile Thr Asn Ala Ile Asp Gly Lys Asn Thr Trp Trp Gln Ser 100 105 110												
Pro Ser Ile Lys Asn Gly Ile Glu Tyr His Tyr Val Thr Ile Thr Leu 115 120 125												
Asp Leu Gln Gln Val Phe Gln Ile Ala Tyr Val Ile Val Lys Ala Ala 130 135 140												
Asn Ser Pro Arg Pro Gly Asn Trp Ile Leu Glu Arg Ser Leu Asp Asp 145 150 150 155 160												

Val Glu Tyr Lys Pro Trp Gln Tyr His Ala Val Thr Asp Thr Glu Cys
165 170 175

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- Lys Asp Asp Glu Val 11e Cys Thr Ser Phe Tyr Ser Lys Ile His Pro 195 200 205
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- Ala Asp Asp Pro Ser Pro Glu Leu Leu Glu Phe Thr Ser Ala Arg Tyr 225 230 235 240
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- Met Phe Ala His Lys Asp Pro Arg Glu Ile Asp Pro Ile Val Thr Arg 260 265 270
- Arg Tyr Tyr Tyr Ser Val Lys Asp Ile Ser Val Gly Gly Met Cys Ile 275 280 285
- Cys Tyr Gly His Ala Arg Ala Cys Pro Leu Asp Pro Ala Thr Asn Lys 290 295 300
- Ser Arg Cys Glu Cys Glu His Asn Thr Cys Gly Asp Ser Cys Asp Gln 305 310 315 320
- Cys Cys Pro Gly Phe His Gln Lys Pro Trp Arg Ala Gly Thr Phe Leu 325 330 335
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- Cys Tyr Tyr Asp Glu Asn Val Ala Arg Arg Asn Leu Ser Leu Asn Ile
- Arg Gly Lys Tyr Ile Gly Gly Gly Val Cys Ile Asn Cys Thr Gln Asn 370 375 380
- Thr Ala Gly Ile Asn Cys Glu Thr Cys Thr Asp Gly Phe Phe Arg Pro 385 390 395 400
- Lys Gly Val Ser Pro Asn Tyr Pro Arg Pro Cys Gln Pro Cys His Cys 405 410 415
- Asp Pro Ile Gly Ser Leu Asn Glu Val Cys Val Lys Asp Glu Lys His
  420 425 430
- Ala Arg Arg Gly Leu Ala Pro Gly Ser Cys His Cys Lys Thr Gly Phe 435  $\phantom{\bigg|}440\phantom{\bigg|}$  445
- Gly Gly Val Ser Cys Asp Arg Cys Ala Arg Gly Tyr Thr Gly Tyr Pro 450 460
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Cys Asp Lys Cys Leu Pro Gly Phe Tyr Gly Glu Pro Thr Lys Gly Thr

Ser Glu Asp Cys Gln Pro Cys Ala Cys Pro Leu Asn Ile Pro Ser Asn

Asn Phe Ser Pro Thr Cys His Leu Asp Arg Ser Leu Gly Leu Ile Cys Asp Gly Cys Pro Val Gly Tyr Thr Gly Pro Arg Cys Glu Arg Cys Ala Glu Gly Tyr Phe Gly Gln Pro Ser Val Pro Gly Gly Ser Cys Gln Pro 855 Cys Gln Cys Asn Asp Asn Leu Asp Phe Ser Ile Pro Gly Ser Cys Asp Ser Leu Ser Gly Ser Cys Leu Ile Cys Lys Pro Gly Thr Thr Gly Arg Tyr Cys Glu Leu Cys Ala Asp Gly Tyr Phe Gly Asp Ala Val Asp Ala 900 905 910 Lys Asn Cys Gln Pro Cys Arg Cys Asn Ala Gly Gly Ser Phe Ser Glu 915 920 925 Val Cys His Ser Gln Thr Gly Gln Cys Glu Cys Arg Ala Asn Val Gln 930 935 940 Gly Gln Arg Cys Asp Lys Cys Lys Ala Gly Thr Phe Gly Leu Gln Ser Ala Arg Gly Cys Val Pro Cys Asn Cys Asn Ser Phe Gly Ser Lys Ser 965 970 975 Phe Asp Cys Glu Glu Ser Gly Gln Cys Trp Cys Gln Pro Gly Val Thr 980 985 990 Gly Lys Lys Cys Asp Arg Cys Ala His Gly Tyr Phe Asn Phe Gln Glu Gly Gly Cys Thr Ala Cys Glu Cys Ser His Leu Gly Asn Asn Cys Asp Pro Lys Thr Gly Arg Cys Ile Cys Pro Pro Asn Thr Ile Gly Glu Lys 1035 Cys Ser Lys Cys Ala Pro Asn Thr Trp Gly His Ser Ile Thr Thr Gly 1045 1050 1055 Cys Lys Ala Cys Asn Cys Ser Thr Val Gly Ser Leu Asp Phe Gln Cys 1065 Asn Val Asn Thr Gly Gln Cys Asn Cys His Pro Lys Phe Ser Gly Ala 1080 Lys Cys Thr Glu Cys Ser Arg Gly His Trp Asn Tyr Pro Arg Cys Asn Leu Cys Asp Cys Phe Leu Pro Gly Thr Asp Ala Thr Thr Cys Asp Ser

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- Ile Val Ala His Met Asp Leu Met Arg Glu Asp Leu His Leu Glu Pro 1220 1225 1230
- Phe Tyr Trp Lys Leu Pro Glu Gln Phe Glu Gly Lys Lys Leu Met Ala 1235 1240 1245
- Tyr Gly Gly Lys Leu Lys Tyr Ala Ile Tyr Phe Glu Ala Arg Glu Glu 1250 1255 1260
- Thr Gly Phe Ser Thr Tyr Asn Pro Gln Val Ile Ile Arg Gly Gly Thr 265 1270 1275 1280
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- Ile Lys Leu Asn Glu Thr Leu Gly Thr Arg Asp Glu Ala Phe Glu Arg 1700 1705 1710
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- Arg Arg Lys Asn Leu Glu Thr Gln Lys Glu Ile Ala Glu Asp Glu Leu 1730 1735 1740
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- Lys Arg Gln Ile Glu Asn Thr Leu Lys Glu Gly Asn Asp Ile Leu Asp 825 1830 1835 1840
- Glu Ala Asn Arg Leu Ala Asp Glu Ile Asn Ser Ile Ile Asp Tyr Val 1845 1850 1855
- Glu Asp Ile Gln Thr Lys Leu Pro Pro Met Ser Glu Glu Leu Asn Asp 1860 1865 1870
- Lys Ile Asp Asp Leu Ser Gln Glu Ile Lys Asp Arg Lys Leu Ala Glu 1875 1880 1885
- Lys Val Ser Gln Ala Glu Ser His Ala Ala Gln Leu Asn Asp Ser Ser 1890 1895 1900
- Ala Val Leu Asp Gly Ile Leu Asp Glu Ala Lys Asn Ile Ser Phe Asn 905 1910 1915 1920
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- Arg Ile Glu Asn Ala Asp Ala Arg Asn Gly Asp Leu Leu Arg Thr Leu 2005 2010 2015
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Leu Lys Pro Ile Lys Glu Leu Glu Asp Asn Leu Lys Lys Asn Ile Ser 2115 2120 2125

- Glu Ile Lys Glu Leu Ile Asn Gln Ala Arg Lys Gln Ala Asn Ser Ile 2130 2135 2140
- Lys Val Ser Val Ser Ser Gly Gly Asp Cys Ile Arg Thr Tyr Lys Pro 145 2150 2155 2160
- Glu Ile Lys Lys Gly Ser Tyr Asn Asn Ile Val Val Asn Val Lys Thr 2165 2170 2175
- Ala Val Ala Asp Asn Leu Leu Phe Tyr Leu Gly Ser Ala Lys Phe Ile 2180 2185 2190
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- Asp Val Gly Ser Gly Val Gly Arg Val Glu Tyr Pro Asp Leu Thr Ile 2210 2215 2220
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- His Asn Asp Gly Lys Trp Lys Ser Phe Thr Leu Ser Arg Ile Gln Lys 2420 2425 2430
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- Ile Asp Glu Lys Leu Met Phe His Val Asp Asn Gly Ala Gly Arg Phe \$2995\$ 3000 3005
- Thr Ala Val Tyr Asp Ala Gly Val Pro Gly His Leu Cys Asp Gly Gln 3010 3015 3020
- Trp His Lys Val Thr Ala Asn Lys Ile Lys His Arg Ile Glu Leu Thr 025 3030 3035 3040
- Val Asp Gly Asn Gln Val Glu Ala Gln Ser Pro Asn Pro Ala Ser Thr 3045 3050 3055
- Ser Ala Asp Thr Asn Asp Pro Val Phe Val Gly Gly Phe Pro Asp Asp 3060 3065 3070
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gaa cat gtc cct ggg cag cct gtg agg aac ccg cag tgt cga atc tgc Glu His Val Pro Gly Gln Pro Val Arg Asn Pro Gln Cys Arg Ile Cys

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Ile Glu Tyr His Tyr Val Thr Ile Thr Leu Asp Leu Gln Gln Val Phe

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aac tgg att ttg gaa cgc tct ctt gat gat gtt gaa tac aag ccc tgg
Asn Trp Ile Leu Glu Arg Ser Leu Asp Asp Val Glu Tyr Lys Pro Trp

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Gln Tyr His Ala Val Thr Asp Thr Glu Cys Leu Thr Leu Tyr Asn Ile

145

150

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165 170 , 175

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		61!	,				020					
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Glu Glu His	Thr Asn	gta ttg Val Lei 630	g tta Leu	Leu aga	Lys aag	Glu 635 gaa	gaa Glu ttt	Ser atg	Phe	Thr gtg	Ile 640 ctt	1920

660 670 gat gcc atc ttc agg ttg agc tct gtt aac ctt gaa tcc gct gtc tcc Asp Ala Ile Phe Arg Leu Ser Ser Val Asn Leu Glu Ser Ala Val Ser 2064 tat cct act gat gga agc att gca gca gct gta gaa gtg tgt cag tgc Tyr Pro Thr Asp Gly Ser Ile Ala Ala Ala Val Glu Val Cys Gln Cys cca cca ggg tat act ggc tcc tct tgt gaa tct tgt tgg cct agg cac Pro Pro Gly Tyr Thr Gly Ser Ser Cys Glu Ser Cys Trp Pro Arg His agg cga gtt aac ggc act att ttt ggt ggc atc tgt gag cca tgt cag Arg Arg Val Asn Gly Thr Ile Phe Gly Gly Ile Cys Glu Pro Cys Gln 725 730 735 aac tgt aag gat cac aca ggt ggc cca tat tgt gat aaa tgt ctt cct Asn Cys Lys Asp His Thr Gly Gly Pro Tyr Cys Asp Lys Cys Leu Pro 755 760 765 2304 ggt ttc tat ggc gag cct act aaa gga acc tct gaa gac tgt caa ccc Gly Phe Tyr Gly Glu Pro Thr Lys Gly Thr Ser Glu Asp Cys Gln Pro tgt gcc tgt cca ctc aat atc cca tcc aat aac ttt agc cca acg tgc Cys Ala Cys Pro Leu Asn Ile Pro Ser Asn Asn Phe Ser Pro Thr Cys 785 790 795 800 2400 cat tta gac cgg agt ctt gga ttg atc tgt gat gga tgc cct gtc ggg His Leu Asp Arg Ser Leu Gly Leu Ile Cys Asp Gly Cys Pro Val Gly 805 810 815 tac aca gga cca ege tgt gag agg tgt gca gaa ggc tat ttt gga caa Tyr Thr Gly Pro Arg Cys Glu Arg Cys Ala Glu Gly Tyr Phe Gly Gln 2496 ccc tct gta cct gga gga tca tgt cag cca tgc caa tgc aat gac aac Pro Ser Val Pro Gly Gly Ser Cys Gln Pro Cys Gln Cys Asn Asp Asn ctt gac ttc tcc atc cct ggc agc tgt gac agc ttg tct ggc tcc tgt 2592 Leu Asp Phe Ser Ile Pro Gly Ser Cys Asp Ser Leu Ser Gly Ser Cys 855 ctg ata tgt aaa cca ggt aca aca ggc cgg tac tgt gag ctc tgt gct Leu Ile Cys Lys Pro Gly Thr Thr Gly Arg Tyr Cys Glu Leu Cys Ala 865 870 875 880 2640 gat gga tat ttt gga gat gca gtt gat gcg aag aac tgt cag ccc tgt 2688 Asp Gly Tyr Phe Gly Asp Ala Val Asp Ala Lys Asn Cys Gln Pro Cys 890 ege tgt aat gee ggt gge tet tte tet gag gtt tge cae agt caa act Arg Cys Asn Ala Gly Gly Ser Phe Ser Glu Val Cys His Ser Gln Thr

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Cys L	ag gc Lys Al 930														2832
	aac tg Asn Cy														2880
	aa tg ln Cy														2928
	gcc ca Ala Hi												Ala		2976
	gt tc Cys Se 99	r His			Asn					Lys					3024
Ile C	ge ce Cys Pr			Thr					Суя						3072
	acc tg Thr Tr		His					Gly					Asn		3120
	aca gt Thr Va	l Gly					Gln					Thr			3168
	aac tg Asn Cy					Ser					Thr				3216
cga g Arg G	ggt ca Gly Hi 107	s Trp	aac Asn	tac Tyr	Pro	cgc Arg L080	tgc Сув	aat Asn	ctc Leu	Сув	gac Asp 1085	tgc Cys	ttc Phe	ctc Leu	3264
Pro G	ggg ac Bly Th			Thr					Glu						3312
	agt ga Ser As		Thr					Сув					Glu		3360
atc c		t gac	aga	tgc	cgg	cct	ggc	aaa	ttc	gga	ctc	gat	gcc	aag	3408
110 1	His Cy	g Asp	Arg 1125	Сув	Arg	Pro		Lув 130	Phe	Gly	Leu		Ala 1135	Lys	

tgc tct g Cys Ser G 11	jaa gca 31u Ala 155	aaa gga Lys Gly	ctg atc Leu Ile 1160	Arg Thr	Trp Val	act ctg Thr Leu 1165	aag gct Lys Ala	3504
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acc aag g Thr Lys G 1185	gc att	gtt ttt Val Phe 1190	caa cat Gln His	Pro Glu	att gtt Ile Val 1195	gcc cac Ala His	atg gac Met Asp 1200	3600
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	-	.203		1000		•	L295	
cga gtc c Arg Val H	at aga	act gtg	Thr Arg	gaa gac		gat ata	cta tat	3936
Arg Val H gat att c Asp Ile H	at aga is Arg 1300	act gtg Thr Val	Thr Arg	gaa gac Glu Asp 305	Phe Leu tat gga Tyr Gly	gat ata Asp Ile 1310	cta tat Leu Tyr atg cga	3936 3984
Arg Val H gat att c Asp Ile H	at aga (is Arg 1300 at tac (is Tyr 15	act gtg Thr Val att ctt Ile Leu tct gaa Ser Glu	Thr Arg  atc aaa Ile Lys 1320 atc tca	gaa gac Glu Asp 305 gct act Ala Thr	Phe Leu tat gga Tyr Gly 1 gta gct	gat ata Asp Ile 1310 aat ttc Asn Phe 325 gaa caa	cta tat Leu Tyr atg cga Met Arg	
gat att c Asp Ile H 13 caa agc a Gln Ser A	eat aga clis Arg 1300 eat tac clis Tyr 15 egg att erg Ile	act gtg Thr Val  att ctt Ile Leu  tct gaa Ser Glu  act cct	atc aaa Ile Lys 1320 atc tca Ile Ser 335 cca gct	gaa gac Glu Asp .305 gct act Ala Thr atg gag Met Glu gac ttg Asp Leu	tat gga Tyr Gly 1 gta gct Val Ala 1340 att gaa	gat ata Asp Ile 1310 aat ttc Asn Phe 325 gaa caa Glu Gln aaa tgt	cta tat Leu Tyr atg cga Met Arg gga cgt Gly Arg	3984
gat att c Asp Ile H 13 caa agc a Gln Ser A 1330 gga aca a Gly Thr T	at aga dis Arg 1300 at tac dis Tyr 15 agg att arg Ile aca atg chr Met agc tat dly Tyr	act gtg Thr Val  att ctt Ile Leu  tct gaa Ser Glu  act cct Thr Pro 1350  tct ggc	Thr Arg atc aaa Ile Lys 1320 atc tca Ile Ser 335 cca gct Pro Ala	gaa gac Glu Asp 305 gct act Ala Thr atg gag Met Glu gac ttg Asp Leu	tat gga Tyr Gly  gta gct Val Ala 1340 att gaa Ile Glu 1355 gca tgc	gat ata Asp Ile 1310 aat ttc Asn Phe 325 gaa caa Glu Gln aaa tgt Lys Cys ttg ccg Leu Pro	cta tat Leu Tyr  atg cga Met Arg  gga cgt Gly Arg  gat tgt Asp Cys 1360  gga ttt	3984 4032
gat att c Asp Ile H 13 caa agc a Gln Ser A 1330 gga aca a Gly Thr T 1345 ccc ctg g	at aga dis Arg 1300  at tac dis Tyr 15  gg att rg fle  ca atg hr Met  gc tat dy Tyr 1  ttg cgt	act gtg Thr Val  att ctt Ile Leu  tct gaa Ser Glu  act cct Thr Pro 1350  tct ggc Ser Gly 365  tct caa	Thr Arg  atc aaa Ile Lys 1320 atc tca Ile Ser 335 cca gct Pro Ala ctg tcc Leu Ser cca ggt	gaa gac Glu Asp 1305  gct act Ala Thr  atg gag Met Glu  gac ttg Asp Leu  1 tgt gag Cys Glu 1370 ggc cgc	tat gga Tyr Gly 1 gta gct Val Ala 1340 att gaa Ile Glu 355 gca tgc Ala Cys acc cct	gat ata Asp Ile 1310 aat ttc Asn Phe 325 gaa caa Glu Gln aaa tgt Lys Cys ttg ccg Leu Pro	cta tat Leu Tyr  atg cga Met Arg  gga cgt Gly Arg  gat tgt Asp Cys 1360  gga ttt Gly Phe 375  acc ctg	3984 4032 4080

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		•		
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aat ctg aat aca	ata ata saa ass	ata asa asa ata	cta acc aga act	4896
Asn Leu Asn Thr 1620	Leu Val Thr Glu	Met Asn Glu Leu 625	Leu Thr Arg Ala 1630	

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caa gaa ata aag gac agg aag ctt gct gag aag gtg tcc cag gct gag
Gln Glu Ile Lys Asp Arg Lys Leu Ala Glu Lys Val Ser Gln Ala Glu
1860 1865 1870

agc cac gca gct cag ttg aat gac tca tct gct gtc ctt gat gga atc
Ser His Ala Ala Gln Leu Asn Asp Ser Ser Ala Val Leu Asp Gly Ile
1875 1880 1885

ctt gat gag gct aaa aac atc tcc t Leu Asp Glu Ala Lys Asn Ile Ser I 1890 1895	
gct tac agc aat att aag gac tat a Ala Tyr Ser Asn Ile Lys Asp Tyr I 1905 1910	
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aat gaa gac cat cta aat ggc tta a Asn Glu Asp His Leu Asn Gly Leu I 1970 1975	
gct aga aat ggg gat ctc ttg aga a Ala Arg Asn Gly Asp Leu Leu Arg T 1985 1990	
tta tca gct att cca aat gat aca g Leu Ser Ala Ile Pro Asn Asp Thr A 2005	
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	Val		aca Thr			Gly					Thr					6864
Lys			ggt Gly		Trp					Lys						6912
gga Gly 230!	Сув	act Thr	gtc Val	Ser	cct Pro 2310	cag Gln	gtg Val	gaa Glu	Asp	agt Ser 2315	gag Glu	gly ggg	act Thr	Ile	caa Gln 2320	6960
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		Ile	tcc Ser 2340				Phe					Phe				7056
	Leu		atg Met			Ala					Arg					7104
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Val Glu Leu Thr Asp Gly His Ile Lys Val Ser Tyr Asp Leu Gly Ser 2370 2375 2380	
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2855

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			hr Gly Val		g atc agt agt / Ile Ser Ser 2960	8880
		y Met Gly I			a aag ttg atg 1 Lys Leu Met 2975	8928
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9420

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Asn Ala Thr Cys Gly Glu Lys Gly Pro Glu Met Tyr Cys Lys Leu Val  $35 \hspace{1cm} 40 \hspace{1cm} 45$ 

Glu His Val Pro Gly Gln Pro Val Arg Asn Pro Gln Cys Arg Ile Cys 50 55 60

Asn Gln Asn Ser Ser Asn Pro Asn Gln Arg His Pro Ile Thr Asn Ala 65 70 75 80

Ile Asp Gly Lys Asn Thr Trp Trp Gln Ser Pro Ser Ile Lys Asn Gly 85 90 95

Ile Glu Tyr His Tyr Val Thr Ile Thr Leu Asp Leu Gln Gln Val Phe 100 \$100\$

Gln Ile Ala Tyr Val Ile Val Lys Ala Ala Asn Ser Pro Arg Pro Gly 115 120 125

Asn Trp 11e Leu Glu Arg Ser Leu Asp Asp Val Glu Tyr Lys Pro Trp 130 135 140

Gln Tyr His Ala Val Thr Asp Thr Glu Cys Leu Thr Leu Tyr Asn Ile 145 150 155 160

Tyr Pro Arg Thr Gly Pro Pro Ser Tyr Ala Lys Asp Asp Glu Val Ile 165  $\phantom{\bigg|}$  170  $\phantom{\bigg|}$  175

Cys Thr Ser Phe Tyr Ser Lys Ile His Pro Leu Glu Asn Gly Glu Ile 180 195 190

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Pro Arg Glu Ile Asp Pro Ile Val Thr Arg Arg Tyr Tyr Tyr Ser Val

Lys Asp Ile Ser Val Gly Gly Met Cys Ile Cys Tyr Gly His Ala Arg 260 265 270

Ala Cys Pro Leu Asp Pro Ala Thr Asn Lys Ser Arg Cys Glu Cys Glu His Asn Thr Cys Gly Asp Ser Cys Asp Gln Cys Cys Pro Gly Phe His 290 295 300 Gln Lys Pro Trp Arg Ala Gly Thr Phe Leu Thr Lys Thr Glu Cys Glu 305 310 315 320Ala Cys Asn Cys His Gly Lys Ala Glu Glu Cys Tyr Tyr Asp Glu Asn Val Ala Arg Arg Asn Leu Ser Leu Asn Ile Arg Gly Lys Tyr Ile Gly Gly Gly Val Cys Ile Asn Cys Thr Gln Asn Thr Ala Gly Ile Asn Cys 355 360 365Glu Thr Cys Thr Asp Gly Phe Phe Arg Pro Lys Gly Val Ser Pro Asn 370 375 380 Tyr Pro Arg Pro Cys Gln Pro Cys His Cys Asp Pro Ile Gly Ser Leu 385 390 395 400 Asn Glu Val Cys Val Lys Asp Glu Lys His Ala Arg Arg Gly Leu Ala 405 410 415 Pro Gly Ser Cys His Cys Lys Thr Gly Phe Gly Gly Val Ser Cys Asp 420 425 430 Arg Cys Ala Arg Gly Tyr Thr Gly Tyr Pro Asp Cys Lys Ala Cys Asn 435 440 445 Cys Ser Gly Leu Gly Ser Lys Asn Glu Asp Pro Cys Phe Gly Pro Cys 450 460 Ile Cys Lys Glu Asn Val Glu Gly Gly Asp Cys Ser Arg Cys Lys Ser 465 470 470 475 Gly Phe Phe Asn Leu Gln Glu Asp Asn Trp Lys Gly Cys Asp Glu Cys 485 490 495Phe Cys Ser Gly Val Ser Asn Arg Cys Gln Ser Ser Tyr Trp Thr Tyr Gly Lys Ile Gln Asp Met Ser Gly Trp Tyr Leu Thr Asp Leu Pro Gly 520 Arg Ile Arg Val Ala Pro Gln Gln Asp Asp Leu Asp Ser Pro Gln Gln Ile Ser Ile Ser Asn Ala Glu Ala Arg Gln Ala Leu Pro His Ser Tyr 545 550 555 560 Tyr Trp Ser Ala Pro Ala Pro Tyr Leu Gly Asn Lys Leu Pro Ala Val Gly Gly Gln Leu Thr Phe Thr Ile Ser Tyr Asp Leu Glu Glu Glu Glu 585

Glu Asp Thr Glu Arg Val Leu Gln Leu Met Ile Ile Leu Glu Gly Asn

Leu Ile Cys Lys Pro Gly Thr Thr Gly Arg Tyr Cys Glu Leu Cys Ala 865 870 875 880

Pro Ser Val Pro Gly Gly Ser Cys Gln Pro Cys Gln Cys Asn Asp Asn

Leu Asp Phe Ser Ile Pro Gly Ser Cys Asp Ser Leu Ser Gly Ser Cys 850 855 860

Asp Gly Tyr Phe Gly Asp Ala Val Asp Ala Lys Asn Cys Gln Pro Cys 885 890 895

Arg Cys Asn Ala Gly Gly Ser Phe Ser Glu Val Cys His Ser Gln Thr 900 905 910

Gly Gln Cys Glu Cys Arg Ala Asn Val Gln Gly Gln Arg Cys Asp Lys 915 920 925

Cys Lys Ala Gly Thr Phe Gly Leu Gln Ser Ala Arg Gly Cys Val Pro 930 935 940

- Cys Asn Cys Asn Ser Phe Gly Ser Lys Ser Phe Asp Cys Glu Glu Ser 945 950 955 960
- Gly Gln Cys Trp Cys Gln Pro Gly Val Thr Gly Lys Lys Cys Asp Arg 965 970 975
- Cys Ala His Gly Tyr Phe Asn Phe Gln Glu Gly Gly Cys Thr Ala Cys 980 985 990
- Glu Cys Ser His Leu Gly Asn Asn Cys Asp Pro Lys Thr Gly Arg Cys 995 1000 1005
- Ile Cys Pro Pro Asn Thr Ile Gly Glu Lys Cys Ser Lys Cys Ala Pro 1010 1015 1020
- Asn Thr Trp Gly His Ser Ile Thr Thr Gly Cys Lys Ala Cys Asn Cys 1025 1030 1035 1040
- Ser Thr Val Gly Ser Leu Asp Phe Gln Cys Asn Val Asn Thr Gly Gln 1045 1050 1055
- Cys Asn Cys His Pro Lys Phe Ser Gly Ala Lys Cys Thr Glu Cys Ser 1060 1065 1070
- Arg Gly His Trp Asn Tyr Pro Arg Cys Asn Leu Cys Asp Cys Phe Leu 1075 1080 1085
- Pro Gly Thr Asp Ala Thr Thr Cys Asp Ser Glu Thr Lys Lys Cys Ser 1090 1095 1100
- Cys Ser Asp Gln Thr Gly Gln Cys Thr Cys Lys Val Asn Val Glu Gly 1105 1110 1115 1120
- Ile His Cys Asp Arg Cys Arg Pro Gly Lys Phe Gly Leu Asp Ala Lys 1125 1130 1135
- Asn Pro Leu Gly Cys Ser Ser Cys Tyr Cys Phe Gly Thr Thr Thr Gln 1140 1145 1150
- Cys Ser Glu Ala Lys Gly Leu Ile Arg Thr Trp Val Thr Leu Lys Ala 1155 1160 1165
- Glu Gln Thr Ile Leu Pro Leu Val Asp Glu Ala Leu Gln His Thr Thr 1170 1175 1180
- Thr Lys Gly Ile Val Phe Gln His Pro Glu Ile Val Ala His Met Asp 1185 1190 1195 1200
- Leu Met Arg Glu Asp Leu His Leu Glu Pro Phe Tyr Trp Lys Leu Pro 1205 1210 1215
- Glu Gln Phe Glu Gly Lys Lys Leu Met Ala Tyr Gly Gly Lys Leu Lys 1220 1225 1230
- Tyr Ala Ile Tyr Phe Glu Ala Arg Glu Glu Thr Gly Phe Ser Thr Tyr 1235 1240 1245

Asn Pro Gln Val Ile Ile Arg Gly Gly Thr Pro Thr His Ala Arg Ile 1250 1255 1260

- Ile Val Arg His Met Ala Ala Pro Leu Ile Gly Gln Leu Thr Arg His 1265 1270 1275 1280
- Glu Ile Glu Met Thr Glu Lys Glu Trp Lys Tyr Tyr Gly Asp Asp Pro 1285 1290 1295
- Arg Val His Arg Thr Val Thr Arg Glu Asp Phe Leu Asp Ile Leu Tyr
  1300 1305 1310
- Asp Ile His Tyr Ile Leu Ile Lys Ala Thr Tyr Gly Asn Phe Met Arg 1315 1320 1325
- Gln Ser Arg Ile Ser Glu Ile Ser Met Glu Val Ala Glu Gln Gly Arg 1330 1335 1340
- Gly Thr Thr Met Thr Pro Pro Ala Asp Leu Ile Glu Lys Cys Asp Cys 1345 1350 1355 1360
- Pro Leu Gly Tyr Ser Gly Leu Ser Cys Glu Ala Cys Leu Pro Gly Phe 1365 1370 1375
- Tyr Arg Leu Arg Ser Gln Pro Gly Gly Arg Thr Pro Gly Pro Thr Leu 1380 1385 1390
- Gly Thr Cys Val Pro Cys Gln Cys Asn Gly His Ser Ser Leu Cys Asp 1395 1400 1405
- Pro Glu Thr Ser Ile Cys Gln Asn Cys Gln His His Thr Ala Gly Asp 1410 1415 1420
- Phe Cys Glu Arg Cys Ala Leu Gly Tyr Tyr Gly Ile Val Lys Gly Leu 1425 1430 1435 1440
- Pro Asn Asp Cys Gln Gln Cys Ala Cys Pro Leu Ile Ser Ser Asn 1445 1450 1455
- Asn Phe Ser Pro Ser Cys Val Ala Glu Gly Leu Asp Asp Tyr Arg Cys 1460 1465 1470
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- Cys Glu Cys Asp Pro Tyr Gly Ser Leu Pro Val Pro Cys Asp Pro Val 1505 1510 1515
- Thr Gly Phe Cys Thr Cys Arg Pro Gly Ala Thr Gly Arg Lys Cys Asp 1525 1530 1535
- Gly Cys Lys His Trp His Ala Arg Glu Gly Trp Glu Cys Val Phe Cys 1540 1545 1550
- Gly Asp Glu Cys Thr Gly Leu Leu Gly Asp Leu Ala Arg Leu Glu \$1555\$ \$1560\$ \$1565\$
- Gln Met Val Met Ser Ile Asn Leu Thr Gly Pro Leu Pro Ala Pro Tyr

1570 1575 1580

Lys Met Leu Tyr Gly Leu Glu Asn Met Thr Gln Glu Leu Lys His Leu 1585 1590 1595 1600

- Leu Ser Pro Gln Arg Ala Pro Glu Arg Leu Ile Gln Leu Ala Glu Gly 1605 1610 1615
- Asn Leu Asn Thr Leu Val Thr Glu Met Asn Glu Leu Leu Thr Arg Ala 1620 1625 1630
- Thr Lys Val Thr Ala Asp Gly Glu Gln Thr Gly Gln Asp Ala Glu Arg 1635 1640 1645
- Thr Asn Thr Arg Ala Lys Ser Leu Gly Glu Phe Ile Lys Glu Leu Ala 1650 1655 1660
- Arg Asp Ala Glu Ala Val Asn Glu Lys Ala Ile Lys Leu Asn Glu Thr 1665 1670 1675 1680
- Leu Gly Thr Arg Asp Glu Ala Phe Glu Arg Asn Leu Glu Gly Leu Gln 1685 1690 1695
- Lys Glu Ile Asp Gln Met Ile Lys Glu Leu Arg Arg Lys Asn Leu Glu 1700 1705 1710
- Thr Gln Lys Glu Ile Ala Glu Asp Glu Leu Val Ala Ala Glu Ala Leu 1715 1720 1725
- Leu Lys Lys Val Lys Lys Leu Phe Gly Glu Ser Arg Gly Glu Asn Glu 1730 1735 1740
- Glu Met Glu Lys Asp Leu Arg Glu Lys Leu Ala Asp Tyr Lys Asn Lys 1745 1750 1755 1760
- Val Asp Asp Ala Trp Asp Leu Leu Arg Glu Ala Thr Asp Lys Ile Arg 1765 1770 1775
- Glu Ala Asn Arg Leu Phe Ala Val Asn Gln Lys Asn Met Thr Ala Leu 1780 1785 1790
- Glu Lys Lys Glu Ala Val Glu Ser Gly Lys Arg Gln Ile Glu Asn 1795 1800 1805
- Thr Leu Lys Glu Gly Asn Asp Ile Leu Asp Glu Ala Asn Arg Leu Ala 1810 1815 1820
- Asp Glu Ile Asn Ser Ile Ile Asp Tyr Val Glu Asp Ile Gln Thr Lys 1825 1830 1835 1840
- Leu Pro Pro Met Ser Glu Glu Leu Asn Asp Lys Ile Asp Asp Leu Ser 1845 1850 1855
- Gln Glu Ile Lys Asp Arg Lys Leu Ala Glu Lys Val Ser Gln Ala Glu 1860 1865 1870
- Ser His Ala Ala Gln Leu Asn Asp Ser Ser Ala Val Leu Asp Gly Ile 1875 1880 1885
- Leu Asp Glu Ala Lys Asn Ile Ser Phe Asn Ala Thr Ala Ala Phe Lys 1890 1895 1900

Ala Tyr Ser Asn Ile Lys Asp Tyr Ile Asp Glu Ala Glu Lys Val Ala 1905 1910 1915 1920

- Lys Glu Ala Lys Asp Leu Ala His Glu Ala Thr Lys Leu Ala Thr Gly 1925 1930 1935
- Pro Arg Gly Leu Leu Lys Glu Asp Ala Lys Gly Cys Leu Gln Lys Ser 1940 1945 1950
- Phe Arg Ile Leu Asn Glu Ala Lys Lys Leu Ala Asn Asp Val Lys Glu 1955 1960 1965
- Asn Glu Asp His Leu Asn Gly Leu Lys Thr Arg Ile Glu Asn Ala Asp 1970 1975 1980
- Ala Arg Asn Gly Asp Leu Leu Arg Thr Leu Asn Asp Thr Leu Gly Lys 1985 1990 1995 2000
- Leu Ser Ala Ile Pro Asn Asp Thr Ala Ala Lys Leu Gln Ala Val Lys 2005 2010 2015
- Asp Lys Ala Arg Gln Ala Asn Asp Thr Ala Lys Asp Val Leu Ala Gln 2020 2025 2030
- Ile Thr Glu Leu His Gln Asn Leu Asp Gly Leu Lys Lys Asn Tyr Asn 2035 2040 2045
- Lys Leu Ala Asp Ser Val Ala Lys Thr Asn Ala Val Val Lys Asp Pro 2050 2060
- Ser Lys Asn Lys Ile Ile Ala Asp Ala Asp Ala Thr Val Lys Asn Leu 2065 2070 2075 2080
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- Asn Gln Ala Arg Lys Gln Ala Asn Ser Ile Lys Val Ser Val Ser Ser 2115 2120 2125
- Gly Gly Asp Cys Ile Arg Thr Tyr Lys Pro Glu Ile Lys Lys Gly Ser 2130 2135 2140
- Tyr Asn Asn Ile Val Val Asn Val Lys Thr Ala Val Ala Asp Asn Leu 2145 2150 2155 2160
- Leu Phe Tyr Leu Gly Ser Ala Lys Phe Ile Asp Phe Leu Ala Ile Glu 2165 2170 2175
- Met Arg Lys Gly Lys Val Ser Phe Leu Trp Asp Val Gly Ser Gly Val 2180 2185 2190
- Gly Arg Val Glu Tyr Pro Asp Leu Thr Ile Asp Asp Ser Tyr Trp Tyr 2195 2200 2205
- Arg Ile Val Ala Ser Arg Thr Gly Arg Asn Gly Thr Ile Ser Val Arg 2210 2215 2220

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- Leu Phe Val Gly Gly Leu Thr Gly Lys Leu Lys Lys Ala Asp Ala Val 2260 2265 2270
- Arg Val Ile Thr Phe Thr Gly Cys Met Gly Glu Thr Tyr Phe Asp Asn 2275 2280 2285
- Lys Pro Ile Gly Leu Trp Asn Phe Arg Glu Lys Glu Gly Asp Cys Lys 2290 2295 2300
- Gly Cys Thr Val Ser Pro Gln Val Glu Asp Ser Glu Gly Thr Ile Gln 2305 2310 2315 2320
- Phe Asp Gly Glu Gly Tyr Ala Leu Val Ser Arg Pro Ile Arg Trp Tyr 2325 2330 2335
- Pro Asn Ile Ser Thr Val Met Phe Lys Phe Arg Thr Phe Ser Ser Ser 2340 2345 2350
- Ala Leu Leu Met Tyr Leu Ala Thr Arg Asp Leu Arg Asp Phe Met Ser 2355 2360 2365
- Val Glu Leu Thr Asp Gly His Ile Lys Val Ser Tyr Asp Leu Gly Ser 2370 2375 2380
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- Lys Ser Phe Thr Leu Ser Arg Ile Gln Lys Gln Ala Asn Ile Ser Ile 2405 2410 2415
- Val Asp Ile Asp Thr Asn Gln Glu Glu Asn Ile Ala Thr Ser Ser Ser 2420 2425 2430
- Gly Asn Asn Phe Gly Leu Asp Leu Lys Ala Asp Asp Lys Ile Tyr Phe 2435 2440 2445
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- Asn Leu Ser Phe Ser Thr Lys Asn Glu Ser Gly Ile Ile Leu Leu Gly 2530 2535 2540
- Ser Gly Gly Thr Pro Ala Pro Pro Arg Arg Lys Arg Arg Gln Thr Gly

2545 2550 2555 2560

- Gln Ala Tyr Tyr Val Ile Leu Leu Asn Arg Gly Arg Leu Glu Val His \$2565\$ \$2570\$ \$2575\$
- Leu Ser Thr Gly Ala Arg Thr Met Arg Lys Ile Val Ile Arg Pro Glu 2580 2585 2590
- Pro Asn Leu Phe His Asp Gly Arg Glu His Ser Val His Val Glu Arg 2595 2600 2605
- Thr Arg Gly Ile Phe Thr Val Gln Val Asp Glu Asn Arg Arg Tyr Met 2610 2615 2620
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- Asp Phe Ala Arg Pro Val Ser Phe Lys Asn Ala Asp Ile Gly Arg Cys 2675 2680 2685
- Ala His Gln Lys Leu Arg Glu Asp Glu Asp Gly Ala Ala Pro Ala Glu 2690 2695 2700
- Ile Val Ile Gln Pro Glu Pro Val Pro Thr Pro Ala Phe Pro Thr Pro 2705 2710 2715 2720
- Thr Pro Val Leu Thr His Gly Pro Cys Ala Ala Glu Ser Glu Pro Ala 2725 2730 2735
- Leu Leu Ile Gly Ser Lys Gln Phe Gly Leu Ser Arg Asn Ser His Ile 2740 2745 2750
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- Pro Tyr Phe Ser Tyr Asp Leu Gly Ser Gly Asp Thr His Thr Met Ile 2805 2810 2815
- Pro Thr Lys Ile Asn Asp Gly Gln Trp His Lys Ile Lys Ile Met Arg 2820 2825 2830
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Thr Tyr Ser Ile Asp Gly Cys Val Arg Asn Leu His Met Ala Glu Ala 2890 Pro Ala Asp Leu Glu Gln Pro Thr Ser Ser Phe His Val Gly Thr Cys 2905 Phe Ala Asn Ala Gln Arg Gly Thr Tyr Phe Asp Gly Thr Gly Phe Ala 2915 2920 2925 Lys Ala Val Gly Gly Phe Lys Val Gly Leu Asp Leu Leu Val Glu Phe 2935 Glu Phe Ala Thr Thr Thr Thr Gly Val Leu Leu Gly Ile Ser Ser Gln Lys Met Asp Gly Met Gly Ile Glu Met Ile Asp Glu Lys Leu Met 2970 Phe His Val Asp Asn Gly Ala Gly Arg Phe Thr Ala Val Tyr Asp Ala Gly Val Pro Gly His Leu Cys Asp Gly Gln Trp His Lys Val Thr Ala 3000 Asn Lys Ile Lys His Arg Ile Glu Leu Thr Val Asp Gly Asn Gln Val Glu Ala Gln Ser Pro Asn Pro Ala Ser Thr Ser Ala Asp Thr Asn Asp 3030 3025 3035 Pro Val Phe Val Gly Gly Phe Pro Asp Asp Leu Lys Gln Phe Gly Leu 3050 3045 Thr Thr Ser Ile Pro Phe Arg Gly Cys Ile Arg Ser Leu Lys Leu Thr Lys Gly Thr Gly Lys Pro Leu Glu Val Asn Phe Ala Lys Ala Leu Glu 3080 Leu <210> 5 <211> 9534 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (50)..(9379)

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46

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														cat His		154
														gct Ala 50		202
														tac Tyr		250
														cag Gln		298
														ccg Pro		346
														agt Ser		394
														tta Leu 130		442
														tcc Ser		490
cgg Arg	cct Pro	gga Gly 150	aac Asn	tgg Trp	att Ile	ttg Leu	gaa G <b>l</b> u 155	cgc Arg	tct Ser	ctt Leu	gat Asp	gat Asp 160	gtt Val	gaa Glu	tac Tyr	538
														acg Thr		586
														gat Asp		634
														gaa Glu 210		682
gga Gly	gag Glu	att Ile	cac His 215	atc Ile	tct Ser	tta Leu	atc Ile	aat Asn 220	61 y 999	aga Arg	cca Pro	agt Ser	gcc Ala 225	gat Asp	gat Asp	730
														cgc Arg		778

aga ttt cag Arg Phe Gl: 245											826
cac aaa ga His Lys As 260											874
tac tcg gto Tyr Ser Va											922
cat gcc agg				o Ala							970
gag tgt gag Glu Cys Glu 31	His Asn					Asp					1018
gga ttc car Gly Phe Hi 325	s Gln Lys	Pro Trp 330	Arg Al	a Gly	Thr	Phe 335	Leu	Thr	Lys	Thr	1066
gaa tgt ga Glu Cys Gl 340	a gca tgc 1 Ala Cys	aat tgt Asn Cys 345	cat gg His Gl	y Lys	gct Ala 350	gaa Glu	gaa Glu	tgc Cys	tat Tyr	tat Tyr 355	1114
gat gaa aa Asp Glu Asi	Val Ala 360	Arg Arg	Asn Le	u Ser 365	Leu	Asn	Ile	Arg	Gly 370	Lys	1162
tac att gg				n Cys							1210
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tct cca aa Ser Pro As 405											1306
ggt tcc tt. Gly Ser Le 420											1354
ggt ttg gc Gly Leu Al											1402
agc tgt ga Ser Cys As				r Thr							1450
gcc tgt aa Ala Cys As: 47	n Cys Ser					Glu					1498
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gat gag tg Asp Glu Cy								1642
tgg acc ta Trp Thr Ty				Ser Gly				1690
ctt cct gg Leu Pro Gl 55	/ Arg Ile							1738
cct cag ca Pro Gln Gl 565			Asn Ala					1786
cac agc ta His Ser Ty 580					Leu Gly			1834
cca gca gt Pro Ala Va								1882
gaa gag ga Glu Glu Gl				Leu Gln				1930
gag ggt aa							ctg :	1978
Glu Gly As 63	n Asp Leu )	Ser Ile	Ser Th	Ala Gln	Asp Glu 640	Val Tyr	Leu	
	gaa gaa	cat act	635 aat gta	ı ttg tta	640 ctt aaa	gaa gaa	tca 2	2026
cac cca tc His Pro Se	gaa gaa Glu Glu	cat act His Thr 650	aat gta Asn Val	a ttg tta Leu Leu a gtc cgt	640 ctt aaa Leu Lys 655 aga aag	gaa gaa Glu Glu gaa ttt	tca 2 Ser	2026 2074
cac cca tc His Pro Se 645  ttt acc at Phe Thr Il	gaa gaa gaa gaa gu Glu ga cat ggc ga His Gly	cat act His Thr 650  aca cat Thr His 665  ttg aag Leu Lys	aat gta Asn Val	a ttg tta Leu Leu a gtc cgt b Val Arg 670 c ctc cta	640  1 ctt aaa 1 Leu Lys 655  2 aga aag Arg Lys	gaa gaa Glu Glu gaa ttt Glu Phe	tca 2 Ser atg 2 Met 675	
cac cca tc His Pro Se 645 ttt acc at Phe Thr I1 660 aca gtg ct	c gaa gaa r Glu Glu a cat ggc e His Gly t gcg aat 1 Ala Asn 680	cat act His Thr 650 aca cat Thr His 665 ttg aag Leu Lys atc ttc	aat gta Asn Va: ttt cca Phe Pro aga gta Arg Va:	a ttg tta Leu Leu a gtc cgt Val Arg 670 c ctc cta Leu Leu 685 g agc tct	640 a ctt aaa a Leu Lys 655 aga aag Arg Lys a caa atc a Gln Ile	gaa gaa Glu Glu gaa ttt Glu Phe aca tac Thr Tyr 690 ctt gaa	tca 2 Ser atg 2 Met 675 agc 2 Ser	2074
cac cca tc His Pro Se 645  ttt acc at Phe Thr I1 660  aca gtg ct Thr Val Le	c gaa gaa r Glu Glu a cat ggc e His Gly t gcg aat 1 Ala Asn 680 g gat gcc t Asp Ala 695 c tat cct	cat act His Thr 650  aca cat Thr His 665  ttg aag Leu Lys  atc ttc Ile Phe	aat gta Asn Va: ttt cca Phe Pro aga gtt Arg Va: agg tta Arg Lei 700	a ttg tta l Leu Leu a gtc cgt b Val Arg 670 c ctc cta l Leu Leu 685 g agc tct s Ser Ser	640  a ctt aaa a Leu Lys 655  aga aag a Arg Lys  a caa atc a Gln Ile  gtt aac val Asn	gaa gaa Glu Glu gaa ttt Glu Phe aca tac Thr Tyr 690 ctt gaa Leu Glu 705	tca 2 Ser atg 2 Met 675 agc 2 Ser tcc 2 Ser gtg 2	207 <b>4</b> 2122

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		Cys			tct Ser		Leu					Asp				3130
	Arg				cca Pro	Pro					Glu					3178
Сув	gca Ala 045	ccc Pro	aat Asn	acc Thr	tgg Trp 1	ggc Gly .050	cac His	agc Ser	att Ile	Thr	act Thr 055	ggt Gly	tgt Cys	aag Lys	gct Ala	3226
	Asn			Thr	gtg Val 1065				Asp					Val		3274
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tgc Cys	Phe	ctc Leu 1110	cct Pro	GJÀ āāā	aca Thr	qaA	gcc Ala 1115	aca Thr	acc Thr	tgt Cys	Asp	tca Ser 1120	gag Glu	act Thr	aaa Lys	3418
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gat Asp	gcc Ala	aag Lys	Asn	cca Pro 1160	ctt Leu	ggc	tgc Cys	Ser	agc Ser 1165	tgc Cys	tat Tyr	tgc Cys	Phe	ggc Gly 1170	act Thr	3562
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His	acg Thr 1205	acc Thr	acc Thr	aag Lys	ggc Gly	att Ile 1210	gtt Val	ttt Phe	caa Gln	His	cca Pro 1215	gag Glu	att Ile	gtt Val	gcc Ala	3706

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			Glu					Lys			atg Met		Tyr			3802
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	Thr					Val					999 Gly 1					3898
Ala					Arg					Pro	ctg Leu L295					3946
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acc agg of Thr Arg A	get acc Ala Thr 1655	aaa gtg Lys Val	Thr Ala	gat ggo Asp Gly 1660	gag cag Glu Gln	acc gga Thr Gly 1665	cag gat Gln Asp	5050
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		ctc cgg gaa aaa c D Leu Arg Glu Lys L 1775	
		g gac ctt ttg aga g o Asp Leu Leu Arg G 1790	
Lys Ile Arg Glu		a ttt gca gta aat c 1 Phe Ala Val Asn G 1805	
		g gct gtt gag agc g 1 Ala Val Glu Ser G 1820	
		c aat gac ata ctc g y Asn Asp Ile Leu A 5 18	
		c atc ata gac tat g r Ile Ile Asp Tyr V 1855	
		t gag gag ctt aat g r Glu Glu Leu Asn A 1870	
Asp Leu Ser Gln		c agg aag ctt gct g p Arg Lys Leu Ala G 1885	
		g ttg aat gac tca t n Leu Asn Asp Ser S 1900	
		a aac atc tcc ttc a s Asn Ile Ser Phe A 5	
		t aag gac tat att g e Lys Asp Tyr Ile A 1935	
		t ctt gca cat gaa g p Leu Ala His Glu A 1950	

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		aag Lys	qaA					Ala					ГЛB			6202
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Ser	gtg Val 2245	aga Arg	gcc Ala	ctg Leu	Asp	gga Gly 250	ccc Pro	aaa Lys	gcc Ala	Ser	att Ile 255	gtg Val	ccc Pro	agc Ser	aca Thr	6826
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Val Glu Arg 2630	Thr Arg G	ly Ile Phe 2635	Thr Val	Gln Val Asp 2640	gaa aac aga Glu Asn Arg	7978
Arg Tyr Met 2645	Gln Asn L	eu Thr Val 2650	Glu Gln	Pro Ile Glu 2655	gtt aaa aag Val Lys Lys	8026
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Asn Ile Pro	Pro Phe G	aa ggc tgc lu Gly Cys	ata tgg Ile Trp	aat ctt gtt Asn Leu Val	att aac tct Ile Asn Ser	8122

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Asn	Ala 50	Leu	Ile	Thr	Thr	Asn 55	Ala	Thr	Сув	Gly	Glu 60	Lys	Gly	Pro	Glu
Met 65	Tyr	Сув	Lув	Leu	Val 70	Glu	His	Val	Pro	Gly 75	Gln	Pro	Val	Arg	neA 08
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Pro	Ser	Ile 115	Lys	Asn	Gly	Ile	Glu 120	Tyr	His	Tyr	Val	Thr 125	Ile	Thr	Leu
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Val	Glu	Tyr	Lys	Pro 165	Trp	Gln	Tyr	His	Ala 170	Val	Thr	qaA	Thr	Glu 175	Сув
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Lys	qeA	Asp 195	Glu	Val	Ile	Сув	Thr 200	Ser	Phe	Tyr	Ser	Lув 205	Ile	aiH	Pro
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Ser 305	Arg	Сув	Glu	Сув	Glu 310	His	Asn	Thr	Cys	Gly 315	Asp	Ser	Сув	Asp	Gln 320
Сув	Суз	Pro	Gly	Phe 325	His	Gln	Lys	Pro	Trp 330	Arg	Ala	Gly	Thr	Phe 335	Leu

Thr Lys Thr Glu Cys Glu Ala Cys Asn Cys His Gly Lys Ala Glu Glu

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Cys Ser Arg Cys Lys Ser Gly Phe Phe Asn Leu Gln Glu Asp Asn Trp 500 505 510

Lys Gly Cys Asp Glu Cys Phe Cys Ser Gly Val Ser Asn Arg Cys Gln 515 520 525

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Leu Thr Asp Leu Pro Gly Arg Ile Arg Val Ala Pro Gln Gln Asp Asp 545 550 550 555

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- Val Ala Glu Gln Gly Arg Gly Thr Thr Met Thr Pro Pro Ala Asp Leu 1365 1370 1375
- Ile Glu Lys Cys Asp Cys Pro Leu Gly Tyr Ser Gly Leu Ser Cys Glu 1380 1385 1390
- Ala Cys Leu Pro Gly Phe Tyr Arg Leu Arg Ser Gln Pro Gly Gly Arg 1395 1400 1405
- Thr Pro Gly Pro Thr Leu Gly Thr Cys Val Pro Cys Gln Cys Asn Gly 1410 1415 1420
- His Ser Ser Leu Cys Asp Pro Glu Thr Ser Ile Cys Gln Asn Cys Gln 425 1430 1435 1440
- His His Thr Ala Gly Asp Phe Cys Glu Arg Cys Ala Leu Gly Tyr Tyr 1445 1450 1455
- Gly Ile Val Lys Gly Leu Pro Asn Asp Cys Gln Gln Cys Ala Cys Pro 1460 1465 1470
- Leu Ile Ser Ser Ser Asn Asn Phe Ser Pro Ser Cys Val Ala Glu Gly 1475 1480 1485
- Leu Asp Asp Tyr Arg Cys Thr Ala Cys Pro Arg Gly Tyr Glu Gly Gln 1490 1495 1500
- Tyr Cys Glu Arg Cys Ala Pro Gly Tyr Thr Gly Ser Pro Gly Asn Pro 505 1510 1515 1520
- Gly Gly Ser Cys Glu Cys Glu Cys Asp Pro Tyr Gly Ser Leu Pro 1525 1530 1535
- Val Pro Cys Asp Pro Val Thr Gly Phe Cys Thr Cys Arg Pro Gly Ala 1540 1545 1550
- Thr Gly Arg Lys Cys Asp Gly Cys Lys His Trp His Ala Arg Glu Gly
- Trp Glu Cys Val Phe Cys Gly Asp Glu Cys Thr Gly Leu Leu Gly 1570 1575 1580
- Asp Leu Ala Arg Leu Glu Gln Met Val Met Ser Ile Asn Leu Thr Gly 585 1590 1595 1600
- Pro Leu Pro Ala Pro Tyr Lys Met Leu Tyr Gly Leu Glu Asn Met Thr 1605 1610 1615
- Gln Glu Leu Lys His Leu Leu Ser Pro Gln Arg Ala Pro Glu Arg Leu 1620 1625 1630

Ile Gln Leu Ala Glu Gly Asn Leu Asn Thr Leu Val Thr Glu Met Asn 1635 1640 1645

- Glu Leu Leu Thr Arg Ala Thr Lys Val Thr Ala Asp Gly Glu Gln Thr 1650 . 1655 1660
- Gly Gln Asp Ala Glu Arg Thr Asn Thr Arg Ala Lys Ser Leu Gly Glu 665 1670 1675 1680
- Phe Ile Lys Glu Leu Ala Arg Asp Ala Glu Ala Val Asn Glu Lys Ala 1685 1690 1695
- Ile Lys Leu Asn Glu Thr Leu Gly Thr Arg Asp Glu Ala Phe Glu Arg 1700 1705 1710
- Asn Leu Glu Gly Leu Gln Lys Glu Ile Asp Gln Met Ile Lys Glu Leu 1715 1720 1725
- Arg Arg Lys Asn Leu Glu Thr Gln Lys Glu Ile Ala Glu Asp Glu Leu 1730 1735 1740
- Val Ala Ala Glu Ala Leu Leu Lys Lys Val Lys Lys Leu Phe Gly Glu
  745 1750 1755 1760
- Ser Arg Gly Glu Asn Glu Glu Met Glu Lys Asp Leu Arg Glu Lys Leu 1765 1770 1775
- Ala Asp Tyr Lys Asn Lys Val Asp Asp Ala Trp Asp Leu Leu Arg Glu 1780 1785 1790
- Ala Thr Asp Lys Ile Arg Glu Ala Asn Arg Leu Phe Ala Val Asn Gln 1795 1800 1805
- Lys Asn Met Thr Ala Leu Glu Lys Lys Lys Glu Ala Val Glu Ser Gly 1810 1815 1820
- Lys Arg Gln Ile Glu Asn Thr Leu Lys Glu Gly Asn Asp Ile Leu Asp 825 1830 1835 1840
- Glu Ala Asn Arg Leu Ala Asp Glu Ile Asn Ser Ile Ile Asp Tyr Val 1845 1850 1855
- Glu Asp Ile Gln Thr Lys Leu Pro Pro Met Ser Glu Glu Leu Asn Asp 1860 1865 1870
- Lys Ile Asp Asp Leu Ser Gln Glu Ile Lys Asp Arg Lys Leu Ala Glu 1875 1880 1885
- Lys Val Ser Gln Ala Glu Ser His Ala Ala Gln Leu Asn Asp Ser Ser 1890 1895 1900
- Ala Val Leu Asp Gly Ile Leu Asp Glu Ala Lys Asn Ile Ser Phe Asn 905 1910 1915 1920
- Ala Thr Ala Ala Phe Lys Ala Tyr Ser Asn Ile Lys Asp Tyr Ile Asp 1925 1930 1935
- Glu Ala Glu Lys Val Ala Lys Glu Ala Lys Asp Leu Ala His Glu Ala 1940 1945 1950
- Thr Lys Leu Ala Thr Gly Pro Arg Gly Leu Leu Lys Glu Asp Ala Lys

1955 1960 1965

- Gly Cys Leu Gln Lys Ser Phe Arg Ile Leu Asn Glu Ala Lys Lys Leu 1970 1975 1980
- Ala Asn Asp Val Lys Glu Asn Glu Asp His Leu Asn Gly Leu Lys Thr 985 1990 1995 2000
- Arg Ile Glu Asn Ala Asp Ala Arg Asn Gly Asp Leu Leu Arg Thr Leu 2005 2010 2015
- Asn Asp Thr Leu Gly Lys Leu Ser Ala Ile Pro Asn Asp Thr Ala Ala 2020 2025 2030
- Lys Leu Gln Ala Val Lys Asp Lys Ala Arg Gln Ala Asn Asp Thr Ala
- Lys Asp Val Leu Ala Gln Ile Thr Glu Leu His Gln Asn Leu Asp Gly 2050 2055 2060
- Leu Lys Lys Asn Tyr Asn Lys Leu Ala Asp Ser Val Ala Lys Thr Asn 065 2070 2075 2080
- Ala Val Val Lys Asp Pro Ser Lys Asn Lys Ile Ile Ala Asp Ala Asp 2085 2090 2095
- Ala Thr Val Lys Asn Leu Glu Gln Glu Ala Asp Arg Leu Ile Asp Lys 2100 2105 2110
- Leu Lys Pro Ile Lys Glu Leu Glu Asp Asn Leu Lys Lys Asn Ile Ser 2115 2120 2125
- Glu Ile Lys Glu Leu Ile Asn Gln Ala Arg Lys Gln Ala Asn Ser Ile 2130 2135 2140
- Lys Val Ser Val Ser Ser Gly Gly Asp Cys Ile Arg Thr Tyr Lys Pro 145 2150 2155 2160
- Glu Ile Lys Lys Gly Ser Tyr Asn Asn Ile Val Val Asn Val Lys Thr 2165 2170 2175
- Ala Val Ala Asp Asn Leu Leu Phe Tyr Leu Gly Ser Ala Lys Phe Ile 2180 2185 2190
- Asp Phe Leu Ala Ile Glu Met Arg Lys Gly Lys Val Ser Phe Leu Trp 2195 2200 2205
- Asp Val Gly Ser Gly Val Gly Arg Val Glu Tyr Pro Asp Leu Thr Ile 2210 2215 2220
- Asp Asp Ser Tyr Trp Tyr Arg Ile Val Ala Ser Arg Thr Gly Arg Asn 225 2230 2235 2240
- Gly Thr Ile Ser Val Arg Ala Leu Asp Gly Pro Lys Ala Ser Ile Val 2245 2250 2255
- Pro Ser Thr His His Ser Thr Ser Pro Pro Gly Tyr Thr Ile Leu Asp
  2260 2265 2270
- Val Asp Ala Asn Ala Met Leu Phe Val Gly Gly Leu Thr Gly Lys Leu 2275 2280 2285

Lys Lys Ala Asp Ala Val Arg Val Ile Thr Phe Thr Gly Cys Met Gly 2290 2295 2300

- Glu Thr Tyr Phe Asp Asn Lys Pro Ile Gly Leu Trp Asn Phe Arg Glu 305 2310 2315 2320
- Lys Glu Gly Asp Cys Lys Gly Cys Thr Val Ser Pro Gln Val Glu Asp 2325 2330 2335
- Ser Glu Gly Thr Ile Gln Phe Asp Gly Glu Gly Tyr Ala Leu Val Ser 2340 2345 2350
- Arg Pro Ile Arg Trp Tyr Pro Asn Ile Ser Thr Val Met Phe Lys Phe 2355 2360 2365
- Arg Thr Phe Ser Ser Ser Ala Leu Leu Met Tyr Leu Ala Thr Arg Asp 2370 2375 2380
- Leu Arg Asp Phe Met Ser Val Glu Leu Thr Asp Gly His Ile Lys Val 385 2390 2395 2400
- Ser Tyr Asp Leu Gly Ser Gly Met Ala Ser Val Val Ser Asn Gln Asn 2405 2410 2415
- His Asn Asp Gly Lys Trp Lys Ser Phe Thr Leu Ser Arg Ile Gln Lys 2420 2425 2430
- Gln Ala Asn Ile Ser Ile Val Asp Ile Asp Thr Asn Gln Glu Glu Asn 2435 2440 2445
- Ile Ala Thr Ser Ser Ser Gly Asn Asn Phe Gly Leu Asp Leu Lys Ala 2450 2455 2460
- Asp Asp Lys Ile Tyr Phe Gly Gly Leu Pro Thr Leu Arg Asn Leu Ser 465 2470 2475 2480
- Met Lys Ala Arg Pro Glu Val Asn Leu Lys Lys Tyr Ser Gly Cys Leu 2485 2490 2495
- Lys Asp Ile Glu Ile Ser Arg Thr Pro Tyr Asn Ile Leu Ser Ser Pro  $2500 \hspace{1cm} 2505 \hspace{1cm} 2510$
- Asp Tyr Val Gly Val Thr Lys Gly Cys Ser Leu Glu Asn Val Tyr Thr \$2515\$ \$2520\$ \$2525\$
- Val Ser Phe Pro Lys Pro Gly Phe Val Glu Leu Ser Pro Val Pro Ile 2530 2535 2540
- Asp Val Gly Thr Glu Ile Asn Leu Ser Phe Ser Thr Lys Asn Glu Ser 545 2550 2555 2560
- Gly Ile Ile Leu Leu Gly Ser Gly Gly Thr Pro Ala Pro Pro Arg Arg 2565 2570 2575
- Lys Arg Arg Gln Thr Gly Gln Ala Tyr Tyr Val Ile Leu Leu Asn Arg 2580 2585 2590
- Gly Arg Leu Glu Val His Leu Ser Thr Gly Ala Arg Thr Met Arg Lys

Ile Val Ile Arg Pro Glu Pro Asn Leu Phe His Asp Gly Arg Glu His . 2610 2615 2620

- Ser Val His Val Glu Arg Thr Arg Gly Ile Phe Thr Val Gln Val Asp 625 2630 2635 2640
- Glu Asn Arg Arg Tyr Met Gln Asn Leu Thr Val Glu Gln Pro Ile Glu 2645 2650 2655
- Val Lys Lys Leu Phe Val Gly Gly Ala Pro Pro Glu Phe Gln Pro Ser 2660 2665 2670
- Pro Leu Arg Asn Ile Pro Pro Phe Glu Gly Cys Ile Trp Asn Leu Val 2675 2680 2685
- Ile Asn Ser Val Pro Met Asp Phe Ala Arg Pro Val Ser Phe Lys Asn 2690 2695 2700
- Ala Asp Ile Gly Arg Cys Ala His Gln Lys Leu Arg Glu Asp Glu Asp 705 2710 2715 2720
- Gly Ala Ala Pro Ala Glu Ile Val Ile Gln Pro Glu Pro Val Pro Thr 2725 2730 2735
- Pro Ala Phe Pro Thr Pro Thr Pro Val Leu Thr His Gly Pro Cys Ala 2740 2745 2750
- Ala Glu Ser Glu Pro Ala Leu Leu Ile Gly Ser Lys Gln Phe Gly Leu 2755 2760 2765
- Ser Arg Asn Ser His Ile Ala Ile Ala Phe Asp Asp Thr Lys Val Lys 2770 2780
- Asn Arg Leu Thr Ile Glu Leu Glu Val Arg Thr Glu Ala Glu Ser Gly 785 2790 2795 2800
- Leu Leu Phe Tyr Met Ala Ala Ile Asn His Ala Asp Phe Ala Thr Val 2805 2810 2815
- Gln Leu Arg Asn Gly Leu Pro Tyr Phe Ser Tyr Asp Leu Gly Ser Gly 2820 2825 2830
- Asp Thr His Thr Met Ile Pro Thr Lys Ile Asn Asp Gly Gln Trp His 2835 2840 2845
- Lys Ile Lys Ile Met Arg Ser Lys Gln Glu Gly Ile Leu Tyr Val Asp 2850 2856
- Gly Ala Ser Asn Arg Thr Ile Ser Pro Lys Lys Ala Asp Ile Leu Asp 865 2870 2875 2880
- Val Val Gly Met Leu Tyr Val Gly Gly Leu Pro Ile Asn Tyr Thr Thr 2885 2890 2895
- Arg Arg Ile Gly Pro Val Thr Tyr Ser Ile Asp Gly Cys Val Arg Asn 2900 2905 2910
- Leu His Met Ala Glu Ala Pro Ala Asp Leu Glu Gln Pro Thr Ser Ser 2915 2920 2925
- Phe His Val Gly Thr Cys Phe Ala Asn Ala Gln Arg Gly Thr Tyr Phe

2935 2940 Asp Gly Thr Gly Phe Ala Lys Ala Val Gly Gly Phe Lys Val Gly Leu 2950 2955 Asp Leu Leu Val Glu Phe Glu Phe Ala Thr Thr Thr Thr Gly Val Leu Leu Gly Ile Ser Ser Gln Lys Met Asp Gly Met Gly Ile Glu Met 2985 Ile Asp Glu Lys Leu Met Phe His Val Asp Asn Gly Ala Gly Arg Phe 3000 Thr Ala Val Tyr Asp Ala Gly Val Pro Gly His Leu Cys Asp Gly Gln 3015 Trp His Lys Val Thr Ala Asn Lys Ile Lys His Arg Ile Glu Leu Thr Val Asp Gly Asn Gln Val Glu Ala Gln Ser Pro Asn Pro Ala Ser Thr 3050 Ser Ala Asp Thr Asn Asp Pro Val Phe Val Gly Gly Phe Pro Asp Asp 3065 Leu Lys Gln Phe Gly Leu Thr Thr Ser Ile Pro Phe Arg Gly Cys Ile Arg Ser Leu Lys Leu Thr Lys Gly Thr Ala Ser His Trp Arg Leu Ile 3095 Leu Pro Arg Pro Trp Asn <210> 7 <211> 9419 <212> DNA <213> Homo sapiens <220> <221> CDS cag cgg ccg cag cag cag cgg cag tca cag gca cat cag caa aga ggt Gln Arg Pro Gln Gln Arg Gln Ser Gln Ala His Gln Gln Arg Gly tta ttc cct gct gtc ctg aat ctt gct tct aat gct ctt atc acg acc Leu Phe Pro Ala Val Leu Asn Leu Ala Ser Asn Ala Leu Ile Thr Thr aat gca aca tgt gga gaa aaa gga cct gaa atg tac tgc aaa ttg gta Asn Ala Thr Cys Gly Glu Lys Gly Pro Glu Met Tyr Cys Lys Leu Val  $35 \hspace{1.5cm} \textbf{40} \hspace{1.5cm} \textbf{10} \hspace{1.5cm}$ 

gaa cat gtc cct ggg cag cct gtg agg aac ccg cag tgt cga atc tgc Glu His Val Pro Gly Gln Pro Val Arg Asn Pro Gln Cys Arg Ile Cys

			agc Ser													240
			aag Lys													288
			cat His 100													336
			tat Tyr													384
			ttg Leu													432
			gct Ala													480
tat Tyr	ccc Pro	ege Arg	act Thr	ggg Gly 165	cca Pro	ccg Pro	tca Ser	tat Tyr	gcc Ala 170	aaa Lys	gat Asp	gat Asp	gag Glu	gtc Val 175	atc Ile	528
Сув	Thr	Ser	ttt Phe 180	Tyr	Ser	Lys	Ile	His 185	Pro	Leu	Glu	Asn	Gly 190	Glu	Ile	576
cac His	atc Ile	tct Ser 195	tta Leu	atc Ile	aat Asn	G1y 999	aga Arg 200	cca Pro	agt Ser	gcc Ala	gat Asp	gat Asp 205	cct Pro	tct Ser	cca Pro	624
Ğlu	Leu 210	Leu	gaa Glu	Phe	Thr	Ser 215	Ala	Arg	Tyr	Ile	Arg 220	Leu	Arg	Phe	Gln	672
Arg 225	Ile	Arg	aca Thr	Leu	Asn 230	Ala	Asp	Leu	Met	Met 235	Phe	Ala	His	Lys	Asp 240	720
cca Pro	aga Arg	gaa Glu	att Ile	gac Asp 245	ccc Pro	att Ile	gtc Val	acc Thr	aga Arg 250	aga Arg	tat Tyr	tac Tyr	tac Tyr	tcg Ser 255	gtc Val	768
			tca Ser 260													816
Āla	Сув	Pro 275	ctt Leu	Āsp	Pro	Ala	Thr 280	Asn	Lys	Ser	Arg	Сув 285	Glu	Сув	Glu	864
cat His	aac Asn 290	aca Thr	tgt Cys	ggc Gly	gat Asp	agc Ser 295	tgt Cys	gat Asp	cag Gln	tgc Cys	tgt Cys 300	cca Pro	gga Gly	ttc Phe	cat His	912

cag aaa ccc t Gln Lys Pro 3 305						960
gca tgc aat t Ala Cys Asn (	tgt cat gga Cys His Gly 325	aaa gct g Lys Ala G	aa gaa tgc lu Glu Cys 330	tat tat gat Tyr Tyr Asp	gaa aat Glu Asn 335	1008
gtt gcc aga a Val Ala Arg A		Ser Leu A				1056
ggg ggt gtc t Gly Gly Val C 355						1104
gag aca tgt a Glu Thr Cys 1 370			rg Pro Lys			1152
tat cca agg o Tyr Pro Arg I 385						1200
aat gaa gtc t Asn Glu Val (						1248
cct gga tcc t Pro Gly Ser (		Lys Thr G				1296
cgg tgt gcc a Arg Cys Ala A 435						1344
tgc agt ggg t Cys Ser Gly I 450			lu Asp Pro			1392
atc tgc aag g Ile Cys Lys C 465						1440
ggc ttc ttc a Gly Phe Phe A						1488
ttc tgt tca g Phe Cys Ser (		Asn Arg C				1536
ggc aaa ata o Gly Lys Ile o S15						1584
cgc att cga g Arg Ile Arg \ 530			sp Asp Leu			1632
atc agc atc a	agt aac gcg	gag gcc c	gg caa gcc	ctg ccg cac	agc tac	1680

Ile Ser 545	Ile	Ser	Asn	Ala 550	Glu	Ala	Arg	Gln	Ala 555	Leu	Pro	His	Ser	Tyr 560	
tac tgg Tyr Trp	agc Ser	gcg Ala	ccg Pro 565	gct Ala	ccc Pro	tat Tyr	ctg Leu	gga Gly 570	aac Asn	aaa Lys	ctc Leu	cca Pro	gca Ala 575	gta Val	1728
gga gga Gly Gly	Gln	ttg Leu 580	aca Thr	ttt Phe	acc Thr	ata Ile	tca Ser 585	tat Tyr	gac Asp	ctt Leu	gaa Glu	gaa Glu 590	gag Glu	gaa Glu	1776
gaa gat Glu Asp															1824
gac ttg Asp Leu 610	Ser														1872
gaa gaa Glu Glu 625															1920
cat ggc His Gly	aca Thr	His	ttt Phe 645	cca Pro	gtc Val	cgt Arg	aga Arg	aag Lys 650	gaa Glu	ttt Phe	atg Met	aca Thr	gtg Val 655	ctt Leu	1968
gcg aat Ala Asn	Leu														2016
gat gcc Asp Ala	Ile					Ser					Ser				2064
	675					680					685				
tat cct Tyr Pro 690	act :					gca					gtg				2112
Tyr Pro	act f	Asp tat	Gly	Ser ggc	Ile 695 tcc	gca Ala tct	Ala	Ala	Val tct	Glu 700 tgt	gtg Val	Cys	Gln agg	Сув	2112
Tyr Pro 690 cca cca Pro Pro	act thr ggg Gly	Asp tat Tyr aac Asn	Gly act Thr	ggc Gly 710	Ile 695 tcc Ser	gca Ala tct Ser	Ala tgt Cys	Ala gaa Glu ggc	Val tct Ser 715 atc	Glu 700 tgt Cys	gtg Val tgg Trp	Cys cct Pro	Gln agg Arg	Cys cac His 720 cag	
Tyr Pro 690 cca cca Pro Pro 705	ggg Gly gtt Val	tat Tyr aac Asn	Gly act Thr ggc Gly 725 gcg	ggc Gly 710 act Thr	lle 695 tcc ser att lle	gca Ala tct Ser ttt Phe	Ala tgt Cys ggt Gly	Ala gaa Glu ggc Gly 730 gac	Val tct Ser 715 atc Ile	Glu 700 tgt Cys tgt Cys	gtg Val tgg Trp gag Glu	Cys cct Pro cca Pro	gln agg Arg tgt Cys 735	Cys cac His 720 cag Gln	2160
Tyr Pro 690 cca cca Pro Pro 705 agg cga Arg Arg	ggg Gly Val	tat Tyr aac Asn cat His 740	Gly act Thr ggc Gly 725 gcg Ala	ggc Gly 710 act Thr gag Glu aca	lle 695 tcc ser att Ile tcc ser	gca Ala tct Ser ttt Phe tgt Cys	Ala tgt Cys ggt Gly gat Asp 745 cca	Ala gaa Glu ggc Gly 730 gac Asp	Val tct Ser 715 atc Ile gtc Val	Glu 700 tgt Cys tgt Cys act Thr	gtg Val tgg Trp gag Glu gga Gly	Cys cct Pro cca Pro gaa Glu 750	agg Arg tgt Cys 735 tgc Cys	cac His 720 cag Gln ctg Leu	2160 2208
Tyr Pro 690  cca cca Pro Pro 705  agg cga Arg Arg  tgc ttt Cys Phe	ggg Gly gtt Val ggt Gly aag Lys 755 tat Tyr	Asp tat Tyr aac Asn cat His 740 gat Asp	Gly act Thr ggc Gly 725 gcg Ala cac His	ggc Gly 710 act Thr gag Glu aca Thr	Ile 695 tcc Ser att Ile tcc Ser ggt Gly act	gca Ala tct Ser ttt Phe tgt Cys	Ala tgt Cys ggt Gly gat Asp 745 cca Pro	Ala gaa Glu ggc Gly 730 gac Asp tat Tyr	Val  tet Ser 715 atc Ile gtc Val tgt Cys	Glu 700 tgt Cys tgt Cys act Thr gat Asp gaa	gtg Val tgg Trp gag Glu gga Gly aaa Lys 765 gac	Cys cct Pro cca Pro gaa Glu 750 tgt Cys	gln agg Arg tgt Cys 735 tgc Cys ctt Leu caa	Cys  cac His 720  cag Gln  ctg Leu  cct	2160 2208 2256

785	790	795	800
cat tta gac cgg ag His Leu Asp Arg Se 80	Leu Gly Leu Ile	tgt gat gga tgc cct Cys Asp Gly Cys Pro 810	gtc ggg 2448 Val Gly 815
tac aca gga cca cg Tyr Thr Gly Pro Ar 820	tgt gag agg tgt G Cys Glu Arg Cys 825	gca gaa ggc tat ttt Ala Glu Gly Tyr Phe 830	Gly Gln
ccc tct gta cct gg Pro Ser Val Pro Gl 835	a gga tca tgt cag / Gly Ser Cys Gln 840	cca tgc caa tgc aat Pro Cys Gln Cys Asn 845	gac aac 2544 Asp Asn
		gac agc ttg tct ggc Asp Ser Leu Ser Gly 860	
ctg ata tgt aaa cc Leu Ile Cys Lys Pro 865	ggt aca aca ggc Gly Thr Thr Gly 870	cgg tac tgt gag ctc Arg Tyr Cys Glu Leu 875	tgt gct 2640 Cys Ala 880
	Asp Ala Val Asp	gcg aag aac tgt cag Ala Lys Asn Cys Gln 890	
		gag gtt tgc cac agt Glu Val Cys His Ser 910	Gln Thr
		cag ggt cag aga tgt Gln Gly Gln Arg Cys 925	
		tca gca agg ggc tgt Ser Ala Arg Gly Cys 940	
		tca ttc gac tgt gaa Ser Phe Asp Cys Glu 955	
	Gln Pro Gly Val	aca ggg aag aaa tgt Thr Gly Lys Lys Cys 970	
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Glu Cys Ser His Le	Gly Asn Asn Cys 1000	gac cca aag act ggg Asp Pro Lys Thr Gly 1005	Arg Cys
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		ggt tgt aag gct tgt Gly Cys Lys Ala Cys 1035	

agc Ser	aca Thr	gtg Val	Gly	tcc Ser 1045	ttg Leu	gat Asp	ttc Phe	Gln	tgc Cys 1050	aat Asn	gta Val	aat Asn	Thr	ggc Gly 1055	caa Gln	3168
tgc Cys	aac Asn	Сув	cat His 1060	cca Pro	aaa Lys	ttc Phe	Ser	ggt Gly 1065	gca Ala	aaa Lys	tgt Cys	Thr	gag Glu 1070	tgc Cys	agt Ser	3216
cga Arg	Gly	cac His L075	tgg Trp	aac Asn	tac Tyr	cct Pro	cgc Arg 1080	tgc Cys	aat Asn	ctc Leu	Cys	gac Asp 1085	tgc Cys	ttc Phe	ctc Leu	3264
Pro					Thr	acc Thr 1095				Glu						3312
	Ser			Thr		cag Gln			Cys					Glu		3360
atc Ile	cac His	tgt Cys	Asp	aga Arg L125	tgc Cys	cgg Arg	cct Pro	Gly	aaa Lys L130	ttc Phe	gga Gly	ctc Leu	Авр	gcc Ala 1135	aag Lys	3408
		Leu				agc Ser	Сув					Thr				3456
	Ser					ctg Leu					Val					3504
Glu					Pro	ctg Leu L175				Ala						3552
	Lys			Val		caa Gln			Glu					Met		3600
			Glu			cat His		Glu					Lys			3648
		Phe				aag Lys	Leu					Gly				3696
	Ala					gct Ala					Gly					3744
Asn					Ile	cga Arg 1255				Pro						3792
atc Ile 126	Val	agg Arg	cat His	Met	gct Ala 1270	gct Ala	cct Pro	ctg Leu	Ile	ggc Gly 1275	caa Gln	ttg Leu	aca Thr	Arg	cat His 1280	3840

gaa att gaa atg Glu Ile Glu Met	aca gag aaa Thr Glu Lys 1285	gaa tgg aaa Glu Trp Lys 1290	tat tat ggg gat Tyr Tyr Gly Asp	gat cct 3888 Asp Pro 1295
cga gtc cat aga Arg Val His Arg 1300	act gtg acc Thr Val Thr	cga gaa gac Arg Glu Asp 1305	ttc ttg gat ata Phe Leu Asp Ile 1310	: Leu Tyr
gat att cat tac Asp Ile His Tyr 1315	Ile Leu Ile	aaa gct act Lys Ala Thr 1320	tat gga aat tto Tyr Gly Asn Phe 1325	e atg cga 3984 e Met Arg
caa agc agg att Gln Ser Arg Ile 1330	tct gaa atc Ser Glu Ile 1335	tca atg gag Ser Met Glu	gta gct gaa caa Val Ala Glu Glr 1340	gga cgt 4032 Gly Arg
gga aca aca atg Gly Thr Thr Met 1345	act cct cca Thr Pro Pro 1350	Ala Asp Leu	att gaa aaa tgt Ile Glu Lys Cys 355	gat tgt 4080 Asp Cys 1360
ccc ctg ggc tat Pro Leu Gly Tyr				
tat cga ctg cgt Tyr Arg Leu Arg 1380				Thr Leu
ggc acc tgt gtt Gly Thr Cys Val 1395	Pro Cys Gln			
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acg gct tgt cca Thr Ala Cys Pro 1475	Arg Gly Tyr			
cct ggc tat act Pro Gly Tyr Thr 1490				
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aca gga ttc tgc	acg tgc cga	cct gga gcc	acg gga agg aag	tgt gac 4608

Thr Gly Phe Cys Thr	Cys Arg Pro Gly Ala	Thr Gly Arg Lys Cys Asp	
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Gly Cys Lys His Trp :	His Ala Arg Glu Gly	Trp Glu Cys Val Phe Cys	
1540	1545	1550	
gga gat gag tgc act	ggc ctt ctt ctc ggt	gac ttg gct cgc ctg gag	4704
Gly Asp Glu Cys Thr	Gly Leu Leu Leu Gly	Asp Leu Ala Arg Leu Glu	
1555	1560	1565	
cag atg gtc atg agc	atc aac ctc act ggt	ccg ctg cct gcg cca tat	4752
Gln Met Val Met Ser	Ile Asn Leu Thr Gly	Pro Leu Pro Ala Pro Tyr	
1570	1575	1580	
Lys Met Leu Tyr Gly	Leu Glu Asn Met Thr	cag gag cta aag cac ttg Gln Glu Leu Lys His Leu 1595 1600	4800
ctg tca cct cag cgg c	gcc cca gag agg ctt	att cag ctg gca gag ggc	4848
Leu Ser Pro Gln Arg 1	Ala Pro Glu Arg Leu	Ile Gln Leu Ala Glu Gly	
1605	1610	1615	
aat ctg aat aca ctc of Asn Leu Asn Thr Leu 1620	gtg acc gaa atg aac Val Thr Glu Met Asn 1625	gag ctg ctg acc agg gct Glu Leu Leu Thr Arg Ala 1630	4896
acc aaa gtg aca gca g	gat ggc gag cag acc	gga cag gat gct gag agg	4944
Thr Lys Val Thr Ala i	Asp Gly Glu Gln Thr	Gly Gln Asp Ala Glu Arg	
1635	1640	1645	
acc aac aca aga gca a	aag too otg gga gaa	ttc att aag gag ctt gcc	4992
Thr Asn Thr Arg Ala i	Lys Ser Leu Gly Glu	Phe Ile Lys Glu Leu Ala	
1650	1655	1660	
Arg Asp Ala Glu Ala	Val Asn Glu Lys Ala	ata aaa cta aat gaa act Ile Lys Leu Asn Glu Thr 1675 1680	5040
		aat ttg gaa ggg ctt cag Asn Leu Glu Gly Leu Gln	5088
		1695	
aaa gag att gac cag a	atg att aaa gaa ctg	agg agg aaa aat cta gag	5136
Lys Glu Ile Asp Gln 1	Met Ile Lys Glu Leu	Arg Arg Lys Asn Leu Glu	
1700	1705	1710	
Lys Glu Ile Asp Gln I 1700 aca caa aag gaa att s	Met Ile Lys Glu Leu 1705 gct gaa gat gag ttg	agg agg aaa aat cta gag Arg Arg Lys Asn Leu Glu	5136 5184
Lys Glu Ile Asp Gln I 1700 aca caa aag gaa att g Thr Gln Lys Glu Ile i 1715 ctg aaa aaa gtg aag a	Met Ile Lys Glu Leu 1705 gct gaa gat gag ttg Ala Glu Asp Glu Leu 1720 aag ctg ttt gga gag	agg agg aaa aat cta gag Arg Arg Lys Asn Leu Glu 1710 gta gct gca gaa gcc ctt Val Ala Ala Glu Ala Leu	
Lys Glu Ile Asp Gln I 1700  aca caa aag gaa att g Thr Gln Lys Glu Ile i 1715  ctg aaa aaa gtg aag a Leu Lys Lys Val Lys I 1730  gaa atg gag aag gat g Glu Met Glu Lys Asp I	Met Ile Lys Glu Leu 1705 gct gaa gat gag ttg Ala Glu Asp Glu Leu 1720 aag ctg ttt gga gag Lys Leu Phe Gly Glu 1735 ctc cgg gaa aaa ctg Leu Arg Glu Lys Leu	agg agg aaa aat cta gag Arg Arg Lys Asn Leu Glu 1710  gta gct gca gaa gcc ctt Val Ala Ala Glu Ala Leu 1725  tcc cgg ggg gaa aat gaa Ser Arg Gly Glu Asn Glu	5184

1765	1770	1775
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	e ata gac tat gtt gaa gac e lle Asp Tyr Val Glu Asp 1835	
	g gag Ctt aat gat aaa ata a Glu Leu Asn Asp Lys Ile 1850	
	g aag ctt gct gag aag gtg g Lys Leu Ala Glu Lys Val 1865	
	g aat gac tca tct gct gtc 1 Asn Asp Ser Ser Ala Val 1880 1	
	e atc tcc ttc aat gcc act 1 Ile Ser Phe Asn Ala Thr 1895 1900	
	g gac tat att gat gaa gct 3 Asp Tyr Ile Asp Glu Ala 1915	
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cct cgg ggt tta tta aa; Pro Arg Gly Leu Leu Ly 1940	g gaa gat gcc aaa ggc tgt g Glu Asp Ala Lys Gly Cys 1945	ctt cag aaa agc 5856 Leu Gln Lys Ser 1950
	a gcc aag aag tta gca aat 1 Ala Lys Lys Leu Ala Asn 1960 1	
aat gaa gac cat cta aa Asn Glu Asp His Leu As 1970	ggc tta aaa acc agg ata Gly Leu Lys Thr Arg Ile 1975 1980	gaa aat gct gat 5952 Glu Asn Ala Asp
	ttg aga act ttg aat gac Leu Arg Thr Leu Asn Asp 1995	
tta tca gct att cca aa: Leu Ser Ala Ile Pro Ass 2005	gat aca gct gct aaa ctg n Asp Thr Ala Ala Lys Leu 2010	caa gct gtt aag 6048 Gln Ala Val Lys 2015

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att aca gag ctc cac cag aac ctc gat ggc ctg aag aag aat tac aat Ile Thr Glu Leu His Gln Asn Leu Asp Gly Leu Lys Lys Asn Tyr Asn 2035 2040 2045	6144
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gaa Cag gaa gct gac cgg cta ata gat aaa ctc aaa ccc atc aag gaa Glu Gln Glu Ala Asp Arg Leu Ile Asp Lys Leu Lys Pro Ile Lys Glu 2085 2090 2095	6288
ctt gag gat aac cta aag aaa aac atc tct gag ata aag gaa ttg ata Leu Glu Asp Asn Leu Lys Lys Asn Ile Ser Glu Ile Lys Glu Leu Ile 2100 2105 2110	6336
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Gly Arg Val Glu Tyr Pro Asp Leu Thr Ile Asp Asp Ser Tyr Trp Tyr 2195 2200 2205	
Gly Arg Val Glu Tyr Pro Asp Leu Thr Ile Asp Asp Ser Tyr Trp Tyr	6672
Gly Arg Val Glu Tyr Pro Asp Leu Thr Ile Asp Asp Ser Tyr Trp Tyr 2195  cgt atc gta gca tca aga act ggg aga aat gga act att tct gtg aga Arg Ile Val Ala Ser Arg Thr Gly Arg Asn Gly Thr Ile Ser Val Arg	6672 6720

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cgt gtg att aca ttc act ggc tgc atg gga gaa aca tac ttt gac aac Arg Val Ile Thr Phe Thr Gly Cys Met Gly Glu Thr Tyr Phe Asp Asn 2275 2280 2285	6864
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Gly Gly Leu Pro Thr Leu Arg Asn Leu Ser Met Lys Ala Arg Pro Glu 2450 2455 2460	7392
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Arg Thr Pro Tyr Asn Ile Leu Ser Ser Pro Asp Tyr Val Gly Val Thr	7488
2485 2490 2495  aaa gga tgt tcc ctg gag aat gtt tac aca gtt agc ttt cct aag cct	7536

Lys Gly Cys Ser Leu Glu Asn Val Tyr Thr Val Ser Phe Pro Lys Pro 2500 2505 2510	
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Asn Trp Ile Leu Glu Arg Ser Leu Asp Asp Val Glu Tyr Lys Pro Trp Gln Tyr His Ala Val Thr Asp Thr Glu Cys Leu Thr Leu Tyr Asn Ile Tyr Pro Arg Thr Gly Pro Pro Ser Tyr Ala Lys Asp Asp Glu Val Ile Cys Thr Ser Phe Tyr Ser Lys Ile His Pro Leu Glu Asn Gly Glu Ile 180 185 190 His Ile Ser Leu Ile Asn Gly Arg Pro Ser Ala Asp Asp Pro Ser Pro Glu Leu Leu Glu Phe Thr Ser Ala Arg Tyr Ile Arg Leu Arg Phe Gln 215 Arg Ile Arg Thr Leu Asn Ala Asp Leu Met Met Phe Ala His Lys Asp Pro Arg Glu Ile Asp Pro Ile Val Thr Arg Arg Tyr Tyr Ser Val  $245 \hspace{1cm} 250 \hspace{1cm} 255 \hspace{1cm}$ Lys Asp Ile Ser Val Gly Gly Met Cys Ile Cys Tyr Gly His Ala Arg Ala Cys Pro Leu Asp Pro Ala Thr Asn Lys Ser Arg Cys Glu Cys Glu His Asn Thr Cys Gly Asp Ser Cys Asp Gln Cys Cys Pro Gly Phe His 290 295 300 Gln Lys Pro Trp Arg Ala Gly Thr Phe Leu Thr Lys Thr Glu Cys Glu Ala Cys Asn Cys His Gly Lys Ala Glu Glu Cys Tyr Tyr Asp Glu Asn Val Ala Arg Arg Asn Leu Ser Leu Asn Ile Arg Gly Lys Tyr Ile Gly 340 345 350Gly Gly Val Cys Ile Asn Cys Thr Gln Asn Thr Ala Gly Ile Asn Cys 355 360 365Glu Thr Cys Thr Asp Gly Phe Phe Arg Pro Lys Gly Val Ser Pro Asn 370 375 380 Tyr Pro Arg Pro Cys Gln Pro Cys His Cys Asp Pro Ile Gly Ser Leu 385 390 395 400 Asn Glu Val Cys Val Lys Asp Glu Lys His Ala Arg Arg Gly Leu Ala 410 Pro Gly Ser Cys His Cys Lys Thr Gly Phe Gly Gly Val Ser Cys Asp 425 Arg Cys Ala Arg Gly Tyr Thr Gly Tyr Pro Asp Cys Lys Ala Cys Asn 435 440 445

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770 775 780

Cys Ala Cys Pro Leu Asn Ile Pro Ser Asn Asn Phe Ser Pro Thr Cys 785 790 795 800

His Leu Asp Arg Ser Leu Gly Leu Ile Cys Asp Gly Cys Pro Val Gly 805 810 815

Tyr Thr Gly Pro Arg Cys Glu Arg Cys Ala Glu Gly Tyr Phe Gly Gln 820 825 830

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Leu Ile Cys Lys Pro Gly Thr Thr Gly Arg Tyr Cys Glu Leu Cys Ala 865 870 875 880

Asp Gly Tyr Phe Gly Asp Ala Val Asp Ala Lys Asn Cys Gln Pro Cys 885 890 895

Arg Cys Asn Ala Gly Gly Ser Phe Ser Glu Val Cys His Ser Gln Thr 900 905 910

Gly Gln Cys Glu Cys Arg Ala Asn Val Gln Gly Gln Arg Cys Asp Lys 915 920 925

Cys Lys Ala Gly Thr Phe Gly Leu Gln Ser Ala Arg Gly Cys Val Pro 930 940

Cys Asn Cys Asn Ser Phe Gly Ser Lys Ser Phe Asp Cys Glu Glu Ser 945 950 950 955

Gly Gln Cys Trp Cys Gln Pro Gly Val Thr Gly Lys Lys Cys Asp Arg 965 970 975

Cys Ala His Gly Tyr Phe Asn Phe Gln Glu Gly Gly Cys Thr Ala Cys 980 985 990

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Ile Cys Pro Pro Asn Thr Ile Gly Glu Lys Cys Ser Lys Cys Ala Pro 1010 1015 1020

Asn Thr Trp Gly His Ser Ile Thr Thr Gly Cys Lys Ala Cys Asn Cys 1025 1030 1035 1040

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Arg Gly His Trp Asn Tyr Pro Arg Cys Asn Leu Cys Asp Cys Phe Leu 1075 1080 1085

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- Thr Lys Val Thr Ala Asp Gly Glu Gln Thr Gly Gln Asp Ala Glu Arg 1635 1640 1645
- Thr Asn Thr Arg Ala Lys Ser Leu Gly Glu Phe Ile Lys Glu Leu Ala 1650 1655 1660
- Arg Asp Ala Glu Ala Val Asn Glu Lys Ala Ile Lys Leu Asn Glu Thr 1665 1670 1680
- Leu Gly Thr Arg Asp Glu Ala Phe Glu Arg Asn Leu Glu Gly Leu Gln 1695 1690 1695
- Lys Glu Ile Asp Gln Met Ile Lys Glu Leu Arg Arg Lys Asn Leu Glu 1700 1705 1710
- Thr Gln Lys Glu Ile Ala Glu Asp Glu Leu Val Ala Ala Glu Ala Leu 1715 1720 1725
- Leu Lys Lys Val Lys Lys Leu Phe Gly Glu Ser Arg Gly Glu Asn Glu 1730 1735 1740
- Glu Met Glu Lys Asp Leu Arg Glu Lys Leu Ala Asp Tyr Lys Asn Lys

1745 1750 1755 1760

- Val Asp Asp Ala Trp Asp Leu Leu Arg Glu Ala Thr Asp Lys Ile Arg 1765 1770 1775
- Glu Ala Asn Arg Leu Phe Ala Val Asn Gln Lys Asn Met Thr Ala Leu 1780 1785 1790
- Glu Lys Lys Clu Ala Val Glu Ser Gly Lys Arg Gln Ile Glu Asn 1795 1800 1805
- Thr Leu Lys Glu Gly Asn Asp Ile Leu Asp Glu Ala Asn Arg Leu Ala 1810 1815 1820
- Asp Glu Ile Asn Ser Ile Ile Asp Tyr Val Glu Asp Ile Gln Thr Lys 1825 1830 1835 1840
- Leu Pro Pro Met Ser Glu Glu Leu Asn Asp Lys Ile Asp Asp Leu Ser 1845 1850 1855
- Gln Glu Ile Lys Asp Arg Lys Leu Ala Glu Lys Val Ser Gln Ala Glu 1860 1865 1870
- Ser His Ala Ala Gln Leu Asn Asp Ser Ser Ala Val Leu Asp Gly Ile 1875 1880 1885
- Leu Asp Glu Ala Lys Asn Ile Ser Phe Asn Ala Thr Ala Ala Phe Lys 1890 1895 1900
- Ala Tyr Ser Asn Ile Lys Asp Tyr Ile Asp Glu Ala Glu Lys Val Ala 1905 1910 1915 1920
- Lys Glu Ala Lys Asp Leu Ala His Glu Ala Thr Lys Leu Ala Thr Gly
- Pro Arg Gly Leu Leu Lys Glu Asp Ala Lys Gly Cys Leu Gln Lys Ser 1940 1945 1950
- Phe Arg Ile Leu Asn Glu Ala Lys Lys Leu Ala Asn Asp Val Lys Glu 1955 1960 1965
- Asn Glu Asp His Leu Asn Gly Leu Lys Thr Arg Ile Glu Asn Ala Asp 1970 1975 1980
- Ala Arg Asn Gly Asp Leu Leu Arg Thr Leu Asn Asp Thr Leu Gly Lys
- Leu Ser Ala Ile Pro Asn Asp Thr Ala Ala Lys Leu Gln Ala Val Lys 2005 2010 2015
- Asp Lys Ala Arg Gln Ala Asn Asp Thr Ala Lys Asp Val Leu Ala Gln 2020 2025 2030
- Ile Thr Glu Leu His Gln Asn Leu Asp Gly Leu Lys Lys Asn Tyr Asn 2035 2040 2045
- Lys Leu Ala Asp Ser Val Ala Lys Thr Asn Ala Val Val Lys Asp Pro 2050 2055 2060
- Ser Lys Asn Lys Ile Ile Ala Asp Ala Asp Ala Thr Val Lys Asn Leu 2065 2070 2075 2080

Glu Gln Glu Ala Asp Arg Leu Ile Asp Lys Leu Lys Pro Ile Lys Glu 2085 2090 2095

- Leu Glu Asp Asn Leu Lys Lys Asn Ile Ser Glu Ile Lys Glu Leu Ile 2100 2105 2110
- Asn Gln Ala Arg Lys Gln Ala Asn Ser Ile Lys Val Ser Val Ser Ser 2115 . 2120 2125
- Gly Gly Asp Cys Ile Arg Thr Tyr Lys Pro Glu Ile Lys Lys Gly Ser 2130 2135 2140
- Tyr Asn Asn Ile Val Val Asn Val Lys Thr Ala Val Ala Asp Asn Leu 2145 2150 2155 2160
- Leu Phe Tyr Leu Gly Ser Ala Lys Phe Ile Asp Phe Leu Ala Ile Glu 2165 2170 2175
- Met Arg Lys Gly Lys Val Ser Phe Leu Trp Asp Val Gly Ser Gly Val 2180 2185 2190
- Gly Arg Val Glu Tyr Pro Asp Leu Thr Ile Asp Asp Ser Tyr Trp Tyr 2195 2200 2205
- Arg Ile Val Ala Ser Arg Thr Gly Arg Asn Gly Thr Ile Ser Val Arg 2210 2215 2220
- Ala Leu Asp Gly Pro Lys Ala Ser Ile Val Pro Ser Thr His His Ser 2225 2230 2235 2240
- Thr Ser Pro Pro Gly Tyr Thr Ile Leu Asp Val Asp Ala Asn Ala Met 2245 2250 2255
- Leu Phe Val Gly Gly Leu Thr Gly Lys Leu Lys Lys Ala Asp Ala Val 2260 2265 2270
- Arg Val Ile Thr Phe Thr Gly Cys Met Gly Glu Thr Tyr Phe Asp Asn  $2275 \hspace{1.5cm} 2280 \hspace{1.5cm} 2285$
- Lys Pro Ile Gly Leu Trp Asn Phe Arg Glu Lys Glu Gly Asp Cys Lys 2290 2295 2300
- Gly Cys Thr Val Ser Pro Gln Val Glu Asp Ser Glu Gly Thr Ile Gln 2305 2310 2315 . 2320
- Phe Asp Gly Glu Gly Tyr Ala Leu Val Ser Arg Pro Ile Arg Trp Tyr 2325 2330 2335
- Pro Asn Ile Ser Thr Val Met Phe Lys Phe Arg Thr Phe Ser Ser Ser 2340 2345 2350
- Ala Leu Leu Met Tyr Leu Ala Thr Arg Asp Leu Arg Asp Phe Met Ser 2355 2360 2365
- Val Glu Leu Thr Asp Gly His Ile Lys Val Ser Tyr Asp Leu Gly Ser 2370 2375 2380
- Gly Met Ala Ser Val Val Ser Asn Gln Asn His Asn Asp Gly Lys Trp 2385 2390 2395 2400

Lys Ser Phe Thr Leu Ser Arg Ile Gln Lys Gln Ala Asn Ile Ser Ile 2405 2410 2415

- Val Asp Ile Asp Thr Asn Gln Glu Glu Asn Ile Ala Thr Ser Ser Ser 2420 2425 2430
- Gly Asn Asn Phe Gly Leu Asp Leu Lys Ala Asp Asp Lys Ile Tyr Phe 2435 2440 2445
- Gly Gly Leu Pro Thr Leu Arg Asn Leu Ser Met Lys Ala Arg Pro Glu 2450 2460
- Val Asn Leu Lys Lys Tyr Ser Gly Cys Leu Lys Asp Ile Glu Ile Ser 2465 2470 2475 2480
- Arg Thr Pro Tyr Asn Ile Leu Ser Ser Pro Asp Tyr Val Gly Val Thr 2485 2490 2495
- Lys Gly Cys Ser Leu Glu Asn Val Tyr Thr Val Ser Phe Pro Lys Pro 2500 2505 2510
- Gly Phe Val Glu Leu Ser Pro Val Pro Ile Asp Val Gly Thr Glu Ile 2515 2520 2525
- Asn Leu Ser Phe Ser Thr Lys Asn Glu Ser Gly Ile Ile Leu Leu Gly 2530 2535 2540
- Ser Gly Gly Thr Pro Ala Pro Pro Arg Arg Lys Arg Arg Gln Thr Gly 2545 2550 2555 2560
- Gln Ala Tyr Tyr Val Ile Leu Leu Asn Arg Gly Arg Leu Glu Val His
- Leu Ser Thr Gly Ala Arg Thr Met Arg Lys Ile Val Ile Arg Pro Glu 2580 2585 2590
- Pro Asn Leu Phe His Asp Gly Arg Glu His Ser Val His Val Glu Arg 2595 2600 2605
- Thr Arg Gly Ile Phe Thr Val Gln Val Asp Glu Asn Arg Arg Tyr Met 2610 2615 2620
- Gln Asn Leu Thr Val Glu Gln Pro Ile Glu Val Lys Lys Leu Phe Val 2625 2630 2635 2640
- Gly Gly Ala Pro Pro Glu Phe Gln Pro Ser Pro Leu Arg Asn Ile Pro 2645 2650 2655
- Pro Phe Glu Gly Cys Ile Trp Asn Leu Val Ile Asn Ser Val Pro Met  $2660 \\ \hspace{1.5cm} 2665 \\ \hspace{1.5cm} 2670 \\ \hspace{1.5cm}$
- Asp Phe Ala Arg Pro Val Ser Phe Lys Asn Ala Asp Ile Gly Arg Cys 2675 2680 2685
- Ala His Gln Lys Leu Arg Glu Asp Glu Asp Gly Ala Ala Pro Ala Glu 2690 2695 2700
- Ile Val Ile Gln Pro Glu Pro Val Pro Thr Pro Ala Phe Pro Thr Pro 2705 2710 2715 2720
- Thr Pro Val Leu Thr His Gly Pro Cys Ala Ala Glu Ser Glu Pro Ala

2725 2730 2735

Leu Leu Ile Gly Ser Lys Gln Phe Gly Leu Ser Arg Asn Ser His Ile \$2740\$ \$2745\$ \$2750

- Ala Ile Ala Phe Asp Asp Thr Lys Val Lys Asn Arg Leu Thr Ile Glu 2755 2760 2765
- Leu Glu Val Arg Thr Glu Ala Glu Ser Gly Leu Leu Phe Tyr Met Ala 2770 2785
- Ala Ile Asn His Ala Asp Phe Ala Thr Val Gln Leu Arg Asn Gly Leu 2785 2790 2795 2800
- Pro Tyr Phe Ser Tyr Asp Leu Gly Ser Gly Asp Thr His Thr Met Ile 2805 2810 2815
- Pro Thr Lys Ile Asn Asp Gly Gln Trp His Lys Ile Lys Ile Met Arg 2820 2825 2830
- Ser Lys Gln Glu Gly Ile Leu Tyr Val Asp Gly Ala Ser Asn Arg Thr 2835 2840 2845
- Ile Ser Pro Lys Lys Ala Asp Ile Leu Asp Val Val Gly Met Leu Tyr 2850 2855 2860
- Val Gly Gly Leu Pro Ile Asn Tyr Thr Thr Arg Arg Ile Gly Pro Val 2865 2870 2875 2880
- Thr Tyr Ser Ile Asp Gly Cys Val Arg Asn Leu His Met Ala Glu Ala 2885 2890 2895
- Pro Ala Asp Leu Glu Gln Pro Thr Ser Ser Phe His Val Gly Thr Cys 2900 2905 2910
- Phe Ala Asn Ala Gln Arg Gly Thr Tyr Phe Asp Gly Thr Gly Phe Ala 2915 2920 2925
- Lys Ala Val Gly Gly Phe Lys Val Gly Leu Asp Leu Leu Val Glu Phe 2930 2940
- Glu Phe Ala Thr Thr Thr Thr Gly Val Leu Leu Gly Ile Ser Ser 2945 2950 2955 2960
- Gln Lys Met Asp Gly Met Gly Ile Glu Met Ile Asp Glu Lys Leu Met 2965 2970 2975
- Phe His Val Asp Asn Gly Ala Gly Arg Phe Thr Ala Val Tyr Asp Ala 2980 2985 2990
- Gly Val Pro Gly His Leu Cys Asp Gly Gln Trp His Lys Val Thr Ala 2995 3000 3005
- Asn Lys Ile Lys His Arg Ile Glu Leu Thr Val Asp Gly Asn Gln Val 3010 3015 3020
- Glu Ala Gln Ser Pro Asn Pro Ala Ser Thr Ser Ala Asp Thr Asn Asp 3025 3030 3035 3040
- Pro Val Phe Val Gly Gly Phe Pro Asp Asp Leu Lys Gln Phe Gly Leu 3045 3050 3055

Thr Thr Ser Ile Pro Phe Arg Gly Cys Ile Arg Ser Leu Lys Leu Thr 3060 Lys Gly Thr Ala Ser His Trp Arg Leu Ile Leu Pro Arg Pro Trp Asn <210> 9 <211> 9511 <212> DNA <213> Mus musculus <220> <221> CDS <222> (55)..(9372) <221> sig\_peptide <222> (55)..(120) ggcacgagct gcaactccgt gggctccggg aggagtggat ctgctccggc cagg atg cct gcg gcc acc gcc ggg atc ctc ttg ctc ctg ctc ttg ggg acg ctc Pro Ala Ala Thr Ala Gly Ile Leu Leu Leu Leu Leu Gly Thr Leu gaa ggc tcc cag act cag cgg cga cag tcc caa gcg cat caa cag aga Glu Gly Ser Gln Thr Gln Arg Arg Gln Ser Gln Ala His Gln Gln Arg ggt tta ttt cct gct gtc ctg aat ctt gct tcg aat gca ctc atc aca Gly Leu Phe Pro Ala Val Leu Asn Leu Ala Ser Asn Ala Leu Ile Thr acc aat gct aca tgt ggg gaa aaa gga ccc gag atg tac tgc aag ttg Thr Asn Ala Thr Cys Gly Glu Lys Gly Pro Glu Met Tyr Cys Lys Leu 50 55 60 65 gtg gaa cat gtc ccc ggg cag cct gtg agg aac cct cag tgc cga atc Val Glu His Val Pro Gly Gln Pro Val Arg Asn Pro Gln Cys Arg Ile 70 75 80 297

gct att gat ggc aag aac aca tgg tgg cag agt ccc agt atc aag aat Ala Ile Asp Gly Lys Asn Thr Trp Trp Gln Ser Pro Ser Ile Lys Asn

393

gga gtg gaa tac cat tat gtg aca att act ctg gat tta cag cag gtg Gly Val Glu Tyr His Tyr Val Thr Ile Thr Leu Asp Leu Gln Gln Val 120

tgc aat cag aac agc agc aat cca tac cag agg cac ccg att acg aat Cys Asn Gln Asn Ser Ser Asn Pro Tyr Gln Arg His Pro Ile Thr Asn

ttc cag att gcc tac gta att gtg aag gca gcc aat tcc cct cgg cct Phe Gln Ile Ala Tyr Val Ile Val Lys Ala Ala Asn Ser Pro Arg Pro 489 135 140

	aac Asn															537
tgg Trp	cag Gln	tat Tyr	cat His 165	gcg Ala	gtg Val	aca Thr	gac Asp	acg <b>Th</b> r 170	gag Glu	tgc Cys	ctg Leu	acc Thr	ctc Leu 175	tac Tyr	aat <b>As</b> n	585
	tat Tyr															633
	tgc Cys 195															681
	cac His															729
	gaa Glu															777
	agg Arg															825
	ccc Pro															873
gtc Val	aag Lys 275	gat Asp	att Ile	tca Ser	gtt Val	ggc Gly 280	Gly 999	atg Met	tgc Cys	atc Ile	tgt Cys 285	tat Tyr	ggt Gly	cat His	gcc Ala	921
	gct Ala															969
	cat His															1017
	cag Gln															1065
	gca Ala															1113
	gtt Val 355															1161
	ggg Gly															1209

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aaa c Lys F 4	cct Pro 435	gga Gly	tcc Ser	tgt Cys	cac His	tgc Cys 440	aaa Lys	act Thr	Gly	ttt Phe	gga Gly 445	ggc	gtg Val	aac Asn	tgt Cys	1401
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aac t Asn C																1497
tgt a Cys S																1545
tct g Ser G																1593
tgt t Cys F																1641
Tyr G																1689
Gly A																1737
cag a Gln I																1785
tac t Tyr T																1833
gtt g Val G	999 31y 595	gga Gly	cag Gln	ttg Leu	tca Ser	ttt Phe 600	acc Thr	atc Ile	tca Ser	tat Tyr	gac Asp 605	ctc Leu	gaa Glu	gaa Glu	gag Glu	1881
gaa g Glu A 610																1929
aat g	gac	tta	aga	atc	agc	aca	gcg	tat	aag	gag	gtg	tac	tta	gag	cca	1977

Asn Asp Leu A	rg Ile Ser 630	Thr Ala T	Tyr Lys Glu 635	Val Tyr Le	u Glu Pr 640	·o
tct gaa gaa ca Ser Glu Glu H: 64		Glu Val S			a Phe Th	
ata cat gga ac Ile His Gly Tl 660						
ctc aca aat te Leu Thr Asn Le 675			le Gln Ile			
atg gac gcc at Met Asp Ala II 690						1
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tgt cca cct gg Cys Pro Pro G		Gly Ser S			p Pro Ar	
cac cga aga gt His Arg Arg Va 740						
cag tgc ttt gc Gln Cys Phe Al 755			ys Asp Asp			
ctg aac tgt aa			gg ccg tac			
Leu Asn Cys Ly	775 ASP H18	Thr Gly G	Tyr 780	Cys Asn Gl	u Cys Le 78	
Leu Asn Cys Ly	775 at ggt gat	cct act c	780 ga gga agc	cct gaa ga	78 c tgt ca	s g 2457
Leu Asn Cys Ly 770  cct gga ttc ta	775 at ggt gat yr Gly Asp 790 gt cca ctc ys Pro Leu	cct act c Pro Thr A aat atc c Asn Ile P	780 ga gga agc arg Gly Ser 795	cct gaa ga Pro Glu As	c tgt ca p Cys Gl 800 t cca ac r Pro Th	5 g 2457 n a 2505
Leu Asn Cys Ly 770  cct gga ttc ta Pro Gly Phe Ty  ccc tgt gcc tg Pro Cys Ala Cy	at ggt gat /r Gly Asp 790 gt cca ctc /s Pro Leu 05	cct act c Pro Thr A aat atc c Asn Ile P 8	rga gga agc lrg Gly Ser 795 ca tca aat Pro Ser Abn 110	cct gaa ga Pro Glu As aac ttt ag Asn Phe Se 81 gac gag tg	78 c tgt ca p Cys Gl 800 t cca ac r Pro Th 5	5 g 2457 n a 2505 r
Leu Asn Cys Ly 770  cct gga ttc ta Pro Gly Phe Ty  ccc tgt gcc tg Pro Cys Ala Cy 80  tgc cat tta ga Cys His Leu As	at ggt gat yr Gly Asp 790 gt cca ctc ys Pro Leu 05 ac cgg agt app Arg Ser ga ccg cgc	cct act c Pro Thr A aat atc c Asn Ile P 8 ctg gga t Leu Gly L 825	gga gga agc rg Gly Ser 795 cca tca aat ro Ser Asn llo ctg atc tgt eu Ile Cys agg tgt gca rg Cys Ala	cct gaa ga Pro Glu As  aac ttt ag Asn Phe Se 81  gac gag tg Asp Glu Cy 830  gaa ggc ta	78 c tgt ca p Cys Gl 800 t cca ac r Pro Th 5 t cct at s Pro Il	g 2457 n 2505 r 2553 e 2601
Leu Asn Cys Ly 770  cct gga ttc ta Pro Gly Phe Ty  ccc tgt gcc tg Pro Cys Ala Cy 80  tgc cat tta ga Cys His Leu As 820  ggg tac aca ga Gly Tyr Thr Gi	at ggt gat yr Gly Asp 790 gt cca ctc ys Pro Leu 55 ac cgg agt ap Arg Ser ga ccg cgc yr Pro Arg	cct act c Pro Thr A  aat atc c Asn Ile P 8  ctg gga t Leu Gly L 825  tgt gag a Cys Glu A 840  gga tca t	gga gga agc rg Gly Ser 795 cca tca aat Pro Ser Asn 110 ctg atc tgt reu Ile Cys rgg tgt gca rg Cys Ala	cct gaa ga Pro Glu As  aac ttt ag Asn Phe Se 81  gac gag tg Asp Glu Cy 830  gaa ggc ta Glu Gly Ty 845  tgc caa tg	78 c tgt ca p Cys Gl 800 t cca ac r Pro Th 5 t cct at s Pro Il t ttt gg r Phe Gl	g 2457 n 2505 r 2553 e 2601 y 2649

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gct Ala	gat Asp	900 900	tat Tyr	ttt Phe	gga Gly	gac Asp	gcg Ala 905	gtt Val	aat Asn	aca Thr	aag Lys	aac Asn 910	tgt Cys	caa Gln	cca Pro	2793
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act Thr 930	61A 888	caa Gln	tgt Cys	gag Glu	tgc Cys 935	aga Arg	ccc Pro	aat Asn	gtt Val	cag Gln 940	G1y 999	cgg Arg	cac His	tgt Cys	gac Asp 945	2889
						ttt Phe										2937
ecc Pro	tgc Cys	aac Asn	tgc Cys 965	aat Asn	tct Ser	ttt Phe	gly ggg	tct Ser 970	aag Lys	tcc Ser	ttt Phe	gac Asp	tgt Cys 975	gaa Glu	gca Ala	2985
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	Asp			His		ggc Gly			Cys					ĞÎy		3129
			Pro			acc Thr		Gly					Glu			3177
		Thr				agc Ser	Ile					Lys				3225
	Ser					ttg Leu 1					naA					3273
Gln					Pro	aaa Lys 1080				Met						3321
	Arg			Trp		tat Tyr			Сув					Cys		3369
			Thr			acg Thr		Сув					Arg			3417

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tat aaa cct caa gtt Tyr Lys Pro Gln Val 1270			
att att acc aga cac Ile Ile Thr Arg His 1285		ro Leu Ile Gly Gl	
cat gaa ata gaa atg His Glu Ile Glu Met 1300			r Gly Asp Asp
cct cga atc agt aga Pro Arg Ile Ser Arg 1315			
tat gat att cac tat Tyr Asp Ile His Tyr 1330			
aga caa agc cgc att Arg Gln Ser Arg Ile 1350			

cat Kis	gta Val	tta Leu	gca Ala 365	91 y 99 9	agc Ser	cca Pro	Pro	gca Ala 1370	cac His	ttg Leu	ata Ile	Glu	aga Arg 1375	tgc Cys	gat Asp	4185
tgc Cys	Pro	cct Pro 1380	ggc Gly	tat Tyr	tct Ser	Gly	ttg Leu 1385	tct Ser	tgt Cys	gag Glu	Thr	tgt Cys 1390	gca Ala	cca Pro	gga Gly	4233
Phe		cga Arg			Ser					Arg						4281
	Gly	acc Thr		Val					Asn					Gln		4329
		gag Glu	Thr					Asn					Thr			4377
		tgt Cys					Leu					Ile				4425
	Pro	aat Asn 1460				Pro					Leu					4473
Asn	Asn	ttc Phe														4521
3	L <b>47</b> 5					1480					485	GIG		-2-		
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tgc Cys 1490 gcc	acc Thr ) cca	gcc Ala ggc Gly	tgc Cys tat Tyr	cca Pro J	agg Arg 1495 ggc	ggc Gly agc	tat Tyr cca	gaa Glu agc Ser	gga Gly I agc	cag Gln 500	tac Tyr gga	tgt Cys ggc	gaa Glu tcc Ser	agg Arg tgc	tgt Cys 1505 caa	<b>4569</b> <b>461</b> 7
tgc Cys 1490 gcc Ala gaa	acc Thr ) cca Pro	Ala ggc Gly gag Glu	tgc Cys tat Tyr	cca Pro act Thr	agg Arg 1495 ggc Gly	ggc Gly agc Ser	tat Tyr cca Pro	gaa Glu agc Ser	gga Gly agc Ser .515	cag Gln 500 ccc Pro	tac Tyr gga Gly	tgt Cys ggc Gly ccc Pro	gaa Glu tcc Ser	agg Arg tgc Cys 1520	tgt Cys 1505 caa Gln	
tgc Cys 1490 gcc Ala gaa Glu	acc Thr ) cca Pro tgt Cys aca Thr	Ala ggc Gly gag Glu	tgc Cys tat Tyr tgt Cys 1525	cca Pro act Thr 1510 gac Asp	agg Arg 1495 ggc Gly cct Pro	ggc Gly agc ser tat Tyr	tat Tyr cca Pro ggc Gly	gaa Glu agc Ser tcc Ser 1530	gga Gly agc Ser 515 cta Leu	cag Gln 500 ccc Pro ccg Pro	tac Tyr gga Gly gtt Val	tgt Cys ggc Gly ccc Pro	gaa Glu tcc Ser tgt Cys 1535	agg Arg tgc Cys 1520 gac Asp	tgt Cys L505 caa Gln cgg Arg	4617
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tgc Cys 1490 gcc Ala gaa gtc Val gtc Cys 1570 gag	acc Thr cca Pro tgt Cys aca Thr ggc Gly 5555 gga Gly	ggc Gly gag Glu 1 1 1 5 1 5 1 5 1 5 1 5 1 5 1 5 1 5 1	tgc Cys tat Tyr Stgt Cys L525 ctc Leu gag Glu gag Glu	cca Pro J act Thr 1510 gac Asp tgc Cys cac His	agg Arg L495 ggc Gly cct Pro acg Thr tgg Trp	ggc Gly agc Ser tat Tyr tgc Cys Set Lise Sec Sec Sec Sec Sec Sec Sec Sec Sec Se	tat Tyr cca Pro ggc Gly Cgc Arg L545 gca Ala ctt Leu	gaa Glu agc Ser 1530 cct Pro cgc Arg ctt Leu	gga Gly agc Ser .515 cta Leu gga Gly ctt Leu	cag Gln .5000 ccc Pro ccg Pro gcc Ala ggt Gly 1 1580 ggt	tac Tyr gga Gly gtt Val aca Thr gca Alaa 565 gac Asp	tgt Cys ggc Gly ccc Pro 3 gga Gly 1550 gag Glu ctg	gaa Glu tcc Ser tgt Cys 1535 agg Arg tgt Cys	agg Arg tgc Cys 1520 gac Asp aag Lys gtc Val	tgt Cys 1505 caa Gln cgg Arg tgt Cys ttt Phe	4617 4665 4713 4761

1605	Tyr Gly Leu	Glu Asn Thr 1610	Thr Gln Glu Leu 1615	Lys His
ctg cta tca ccg Leu Leu Ser Pro 1620	Gln Arg Ala	cca gag agg Pro Glu Arg 1625	ctc att cag ttg Leu Ile Gln Leu 1630	gca gag 4953 Ala Glu
ggc aac gtg aac Gly Asn Val Asr 1635	aca ctt gtg Thr Leu Val 1640	atg gaa aca Met Glu Thr	aat gag ctg cta Asn Glu Leu Leu 1645	acc aga 5001 Thr Arg
gca acc aaa gto Ala Thr Lys Val 1650	aca gca gat Thr Ala Asp 1655	Gly Glu Gln	aca gga caa gat Thr Gly Gln Asp .660	gct gag 5049 Ala Glu 1665
agg acc aac too Arg Thr Asn Ser	aga gca gaa Arg Ala Glu 1670	tcc ttg gaa Ser Leu Glu 1675	gaa ttc att aaa Glu Phe Ile Lys	ggg ctt 5097 Gly Leu 1680
	Glu Ala Ile		gct gta aaa cta Ala Val Lys Leu 1695	
	Gln Asp Lys		aga aac ttg gag Arg Asn Leu Glu 1710	
			ctg aga agt aaa Leu Arg Ser Lys 1725	
			ctc gtg gca gca	
1730	1735		Leu Val Ala Ala 740	Glu Gly 1745
1730 ctt ctg aag aga	1735 gta aac aag	ctg ttt gga	740 gag ccc aga gcc Glu Pro Arg Ala	1745 cag aat 5337
ctt ctg aag aga Leu Leu Lys Arc	1735  gta aac aag Val Asn Lys 1750  aag gat ctc Lys Asp Leu	ctg ttt gga Leu Phe Gly 1755	740 gag ccc aga gcc Glu Pro Arg Ala	1745  cag aat 5337 Gln Asn 1760  aag aac 5385
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1845	1850	1855	
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gcc cag gaa ata aag gac Ala Gln Glu Ile Lys Asp 1875	aga agg ctt gct ga Arg Arg Leu Ala Gl 1880	ag aag gtg ttc cag gct lu Lys Val Phe Gln Ala 1885	5721
gag agc cat gct gct cag Glu Ser His Ala Ala Gln 1890 1895	ctg aac gac tcg to Leu Asn Asp Ser Se 190	er Ala Val Leu Asp Gly	5769
atc ctg gat gag gct aag Ile Leu Asp Glu Ala Lys 1910			5817
aga gct tac agt aat att Arg Ala Tyr Ser Asn Ile 1925	aaa gac tac att ga Lys Asp Tyr Ile As 1930	at gaa gct gag aaa gtg sp Glu Ala Glu Lys Val 1935	5865
gcc aga gaa gcc aaa gag Ala Arg Glu Ala Lys Glu 1940			5913
agt cct cag ggc tta tta Ser Pro Gln Gly Leu Leu 1955	aaa gaa gat gcc aa Lys Glu Asp Ala Ly .960	aa ggc tcc ctt cag aaa ys Gly Ser Leu Gln Lys 1965	5961
agc ttc agg atc ctc aat Ser Phe Arg Ile Leu Asn 1970 1975		eu Ala Asn Asp Val Lys	6009
gga aat cac aat gat cta Gly Asn His Asn Asp Leu 1990			6057
gac ctt aga aac agt gga Asp Leu Arg Asn Ser Gly 2005			6105
aag tta tca gcc att aca Lys Leu Ser Ala Ile Thr 2020	aat gac acg gct gc Asn Asp Thr Ala Al 2025	et aaa ctg cag gct gtc La Lys Leu Gln Ala Val 2030	6153
aaa gag aaa gcc aga gaa Lys Glu Lys Ala Arg Glu 2035 2			6201
cag gtt aag gac ctg cat Gln Val Lys Asp Leu His 2050 2055		y Leu Lys Gln Asn Tyr	6249
aat aaa ctg gca gac agc Asn Lys Leu Ala Asp Ser 2070	gtg gcc aaa acg aa Val Ala Lys Thr As 2075	ac gct gtg gtg aaa gat sn Ala Val Val Lys Asp 2080	6297
cct tcc aaa aac aaa atc Pro Ser Lys Asn Lys Ile 2085	att gca gat gca gg Ile Ala Asp Ala Gl 2090	gc act tcc gtg aga aat .y Thr Ser Val Arg Asn 2095	6345

cta c Leu (	31u					Arg					Leu					6393
gag o Glu I 2:					Leu					Ser						6441
atc a Ile A 2130				Arg					Ser					Val		6489
tcg ( Ser (			qaA					Tyr					ГЛВ			6537
agc t Ser :		Asn					His					Val				6585
ctc ( Leu )	Leu					Ser					Asp					6633
gaa a Glu 1 2:	atg Met 195	cgc Arg	aaa Lys	ggc	Lys	gtc Val 200	agc Ser	ttc Phe	ctc Leu	Trp	att Ile 205	gtt Val	ggc Gly	tct Ser	gga Gly	6681
gtt 9 Val 0 2210	Gly	cga Arg	gta Val	Gly	ttt Phe 215	cca Pro	gac Asp	ttg Leu	Thr	atc Ile 2220	gac Asp	gac Asp	tcc Ser	Tyr	tgg Trp 2225	6729
tac (			Glu					Gly					Ile			6777
aga q Arg 2	gct Ala	Leu	gat Asp 245	gga Gly	ccc Pro	aaa Lys	Ala	agt Ser 2250	atg Met	gta Val	ccc Pro	Ser	acc Thr 255	tac Tyr	cat His	6825
tca ( Ser	va i					Tyr					Val					6873
atg Met : 2:					Gly					Ile						6921
gta Val 2290	Arg			Thr					Met					Phe		6969
aac Asn			Ile					Phe					Gly			7017
aag Lys		Cys					Gln					Glu				7065

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Гуr	ccc Pro 355	aac Asn	atc Ile	tcc Ser	Thr	gtc Val 2360	atg Met	ttc Phe	aag Lys	Phe	cgg Arg 365	aca Thr	ttt Phe	tca Ser	tca Ser	7161
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agt Ser	gta Val	gag Glu	Leu	agt Ser 2390	gat Asp	gga Gly	cat His	Val	aaa Lys 395	gtc Val	agc Ser	tat Tyr	qaA	ctg Leu 2400	ggc Gly	7257
		atg Met 2					Ser					Asn				7305
	Lys	gca Ala 420				Ser					Gln					7353
Ile		gac Asp			Ser					Авп						7401
	Gly	aac Asn		Phe					Lys					Ile		7449
		ggc Gly	Leu					Asn					Ala			7497
		aat Asn 2					Ser					Asp				7545
	Arg	aca Thr 500				Ile					Asp					7593
Thr		ggc Gly			Leu					Thr						76 <b>4</b> 1
	Gly	ttt Phe		Glu					Ser					Thr		7689
		ctg Leu	Ser					Asn					Ile			7737
		gga Gly 2					Pro					Arg				7785
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Thr Gln	Ala Ty 2580	r Tyr	Ala Il	e Phe 2585	Leu	Asn	Lys		Arg 2590	Leu	Glu	Val	
cat ctc His Leu 2595	tcc tc Ser Se	a aaa r Gly	aca co Thr Ar 260	g Thr	atg Met	agg Arg	Lys	att Ile 2605	gtc Val	atc Ile	aaa Lys	ccg Pro	7881
gag cca Glu Pro 2610	aat tt Asn Le	u Phe	cat ga His As 2615	t ggg p Gly	aga Arg	Glu	cat His 2620	tct Ser	gtc Val	cac His	Val	gaa Glu 2625	7929
aga acc Arg Thr					Gln					Arg			7977
atc caa Ile Gln		u Thr		u Gln					Lys				8025
	Gly Al 2660	a Pro	Pro Gl	u Phe 2665	Gln	Pro	Ser	Pro	Leu 2670	Arg	Asn	Ile	8073
ecg gee Pro Ala 2675	Phe Gl	n Gly	Cys Va 268	l Trp	Asn	Leu	Val	Ile 2685	Asn	Ser	Ile	Pro	8121
atg gac Met Asp 2690	Phe Al	a Gln	Pro I1 2695	e Ala	Phe	Lys	Asn 2700	Ala	Āsp	Ile	Gly	Arg 2705	8169
tgt acc Cys Thr	Tyr Gl	n Lys 2710	Pro Ar	g Glu	Asp	Glu 2715	Ser	Glu	Ala	Val	Pro 2720	Āla	8217
gaa gtt Glu Val	Ile Va 272	l Gln 5	Pro Gl	n Ser	Val 2730	Pro	Thr	Pro	Āla	Phe 2735	Pro	Phe	8265
	Pro Th 2740	r Met	Val Hi	s Gly 2745	Pro	Cys	Val	Ala	Glu 2750	Ser	Glu	Pro	8313
gct ctt Ala Leu 2755				s Gln			Leu						8361
att gca Ile Ala 2770	att gt Ile Va	l Phe	gat ga Asp As 2775	c acc p Thr	aaa Lys	Val	aaa Lys 2780	aac Asn	cgc Arg	ctc Leu	Thr	att Ile 2785	8409
gag ctg Glu Leu	Glu Va	1 Arg 2790	Thr Gl	u Ala	Glu	Ser 2795	Gly	Leu	Leu	Phe	Tyr 2800	Met	8457
ggt cgg Gly Arg	Ile As 280	n His 5	Ala As	p Phe	Gly 2810	Thr	Val	Gln	Leu 2	Arg 2815	Asn	Gly	8505
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9273

3050

gac cct gtt ttc gtt ggc ggt ttc cca ggt ggc ctc aat cag ttt ggc Asp Pro Val Phe Val Gly Gly Phe Pro Gly Gly Leu Asn Gln Phe Gly

3065

•• .

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acc aaa ggc act Thr Lys Gly Thr 3090	gca aac cg Ala Asn Ar 3095	c tgg agg t g Trp Arg L	ta att ttg cca eu Ile Leu Pro 3100	a agg ccc tgg D Arg Pro Trp 3105	9369
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Arg Gly Leu Phe 35	Pro Ala Va	L Leu Asn Le 40	eu Ala Ser Ası 49		
Thr Thr Asn Ala	Thr Cys Gly		ly Pro Glu Met 60	Tyr Cys Lys	
Leu Val Glu His 65	Val Pro Gly	/ Gln Pro Va	al Arg Asn Pro 75	Gln Cys Arg 80	
Ile Cys Asn Gln	Asn Ser Ser 85		yr Gln Arg His 90	Pro Ile Thr 95	
Asn Ala Ile Asp 100	Gly Lys Ası	Thr Trp Tr 105	rp Gln Ser Pro	Ser Ile Lys 110	
Asn Gly Val Glu 115	Tyr His Tyr	Val Thr II	le Thr Leu Asp 125		
Val Phe Gln Ile 130	Ala Tyr Vai		ys Ala Ala Asr 140	Ser Pro Arg	
Pro Gly Asn Trp 145	Ile Leu Glu 150	Arg Ser Le	eu Asp Asp Val 155	Glu Tyr Lys 160	
Pro Trp Gln Tyr	His Ala Val	Thr Asp Th		Thr Leu Tyr 175	
Asn Ile Tyr Pro 180	Arg Thr Gl	Pro Pro Se 185	er Tyr Ala Lys	Asp Asp Glu 190	
Val Ile Cys Thr 195	Ser Phe Tyr	Ser Lys Il 200	le His Pro Leu 205		

Glu Ile His Ile Ser Leu Ile Asn Gly Arg Pro Ser Ala Asp Asp Pro Ser Pro Glu Leu Leu Glu Phe Thr Ser Ala Arg Tyr Ile Arg Leu Arg 225 230 235 240 Phe Gln Arg Ile Arg Thr Leu Asn Ala Asp Leu Met Met Phe Ala His 245 250 255 Lys Asp Pro Arg Glu Ile Asp Pro Ile Val Thr Arg Arg Tyr Tyr Tyr 260 265 270 Ser Val Lys Asp Ile Ser Val Gly Gly Met Cys Ile Cys Tyr Gly His 275 280 285 Ala Arg Ala Cys Pro Leu Asp Pro Ala Thr Asn Lys Ser Arg Cys Glu 295 Cys Glu His Asn Thr Cys Gly Glu Ser Cys Asp Arg Cys Cys Pro Gly 305 310 315 320 Phe His Gln Lys Pro Trp Arg Ala Gly Thr Phe Leu Thr Lys Ser Glu Cys Glu Ala Cys Asn Cys His Gly Lys Ala Glu Glu Cys Tyr Tyr Asp 340 345 350Glu Thr Val Ala Ser Arg Asn Leu Ser Leu Asn Ile His Gly Lys Tyr 355 360 365 Ile Gly Gly Gly Val Cys Ile Asn Cys Thr His Asn Thr Ala Gly Ile 370 375 380 Asn Cys Glu Thr Cys Val Asp Gly Phe Phe Arg Pro Lys Gly Val Ser 385 390 395 400 Pro Asn Tyr Pro Arg Pro Cys Gln Pro Cys His Cys Asp Pro Thr Gly 405 410 415 Ser Leu Ser Glu Val Cys Val Lys Asp Glu Lys Tyr Ala Gln Arg Gly 420 425 430Leu Lys Pro Gly Ser Cys His Cys Lys Thr Gly Phe Gly Gly Val Asn 435  $\phantom{\bigg|}440\phantom{\bigg|}$ Cys Asp Arg Cys Val Arg Gly Tyr His Gly Tyr Pro Asp Cys Gln Pro 450 455 460 Cys Asn Cys Ser Gly Leu Gly Ser Thr Asn Glu Asp Pro Cys Val Gly Pro Cys Ser Cys Lys Glu Asn Val Glu Gly Glu Asp Cys Ser Arg Cys Lys Ser Gly Phe Phe Asn Leu Gln Glu Asp Asn Gln Lys Gly Cys Glu Glu Cys Phe Cys Ser Gly Val Ser Asn Arg Cys Gln Ser Ser Tyr Trp

Thr Tyr Gly Asn Ile Gln Asp Met Arg Gly Trp Tyr Leu Thr Asp Leu Ser Gly Arg Ile Arg Met Ala Pro Gln Leu Asp Asn Pro Asp Ser Pro Gln Gln Ile Ser Ile Ser Asn Ser Glu Ala Arg Lys Ser Leu Leu Asp 565 570 575 Gly Tyr Tyr Trp Ser Ala Pro Pro Pro Tyr Leu Gly Asn Arg Leu Pro 580 585 590 Ala Val Gly Gln Leu Ser Phe Thr Ile Ser Tyr Asp Leu Glu Glu Glu Glu Asp Asp Thr Glu Lys Leu Leu Gln Leu Met Ile Ile Phe Glu Gly Asn Asp Leu Arg Ile Ser Thr Ala Tyr Lys Glu Val Tyr Leu Glu 625 630 635 640 Pro Ser Glu Glu His Val Glu Glu Val Ser Leu Lys Glu Glu Ala Phe Thr Ile His Gly Thr Asn Leu Pro Val Thr Arg Lys Asp Phe Met Ile Val Leu Thr Asn Leu Gly Glu Ile Leu Ile Gln Ile Thr Tyr Asn Leu 675 680 685 Gly Met Asp Ala Ile Phe Arg Leu Ser Ser Val Asn Leu Glu Ser Pro 690 695 700 Val Pro Tyr Pro Thr Asp Arg Arg Ile Ala Thr Asp Val Glu Val Cys 705 710 715 720 Gln Cys Pro Pro Gly Tyr Ser Gly Ser Ser Cys Glu Thr Cys Trp Pro
725 730 735 Arg His Arg Arg Val Asn Gly Thr Ile Phe Gly Gly Ile Cys Glu Pro  $740 \hspace{1cm} 745 \hspace{1cm} 750 \hspace{1cm} 750 \hspace{1cm}$ Cys Gln Cys Phe Ala His Ala Glu Ala Cys Asp Asp Ile Thr Gly Glu 755 760 765 Cys Leu Asn Cys Lys Asp His Thr Gly Gly Pro Tyr Cys Asn Glu Cys Leu Pro Gly Phe Tyr Gly Asp Pro Thr Arg Gly Ser Pro Glu Asp Cys 785 790 795 800 Gln Pro Cys Ala Cys Pro Leu Asn Ile Pro Ser Asn Asn Phe Ser Pro 805 810 815 Thr Cys His Leu Asp Arg Ser Leu Gly Leu Ile Cys Asp Glu Cys Pro Ile Gly Tyr Thr Gly Pro Arg Cys Glu Arg Cys Ala Glu Gly Tyr Phe Gly Gln Pro Ser Val Pro Gly Gly Ser Cys Gln Pro Cys Gln Cys Asn

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Ala Lys Asn Pro Leu Gly Cys Ser Ser Cys Tyr Cys Phe Gly Val Thr

Ser Gln Cys Ser Glu Ala Lys Gly Leu Ile Arg Thr Trp Val Thr Leu 1170 1175 1180

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- Thr Thr Thr Lys Gly Ile Ala Phe Gln Lys Pro Glu Ile Val Ala Lys 1205 1210 1215
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- Arg Ile Ile Thr Arg His Met Ala Ala Pro Leu Ile Gly Gln Leu Thr 1285 1290 1295
- Arg His Glu Ile Glu Met Thr Glu Lys Glu Trp Lys Tyr Tyr Gly Asp 1300 1305 1310
- Asp Pro Arg Ile Ser Arg Thr Val Thr Arg Glu Asp Phe Leu Asp Ile 1315 1320 1325
- Leu Tyr Asp Ile His Tyr Ile Leu Ile Lys Ala Thr Tyr Gly Asn Val 1330 1335 1340
- Val Arg Gln Ser Arg Ile Ser Glu Ile Ser Met Glu Val Ala Glu Pro 345 1350 1355 1360
- Gly His Val Leu Ala Gly Ser Pro Pro Ala His Leu Ile Glu Arg Cys 1365 1370 1375
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- Gly Phe Tyr Arg Leu Arg Ser Glu Pro Gly Gly Arg Thr Pro Gly Pro 1395 1400 1405
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- Cys Asp Pro Glu Thr Ser Val Cys Gln Asn Cys Gln His His Thr Ala 425 1430 1435 1440
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- Gly Leu Pro Asn Asp Cys Gln Pro Cys Ala Cys Pro Leu Ile Ser Pro 1460 1465 1470
- Ser Asn Asn Phe Ser Pro Ser Cys Val Leu Glu Gly Leu Glu Asp Tyr 1475 1480 1485
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Cys Ala Pro Gly Tyr Thr Gly Ser Pro Ser Ser Pro Gly Gly Ser Cys 505 1510 1515 1520

- Gln Glu Cys Glu Cys Asp Pro Tyr Gly Ser Leu Pro Val Pro Cys Asp · 1525 1530 1535
- Arg Val Thr Gly Leu Cys Thr Cys Arg Pro Gly Ala Thr Gly Arg Lys 1540 1545 1550
- Cys Asp Gly Cys Glu His Trp His Ala Arg Glu Gly Ala Glu Cys Val 1555 1560 1565
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- His Leu Leu Ser Pro Gln Arg Ala Pro Glu Arg Leu Ile Gln Leu Ala 1620 1625 1630
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- Leu Gln Lys Glu Ile Asp Arg Met Leu Lys Glu Leu Arg Ser Lys Asp 1715 1720 1725
- Leu Gln Thr Gln Lys Glu Val Ala Glu Asp Glu Leu Val Ala Ala Glu 1730 1735 1740
- Gly Leu Leu Lys Arg Val Asn Lys Leu Phe Gly Glu Pro Arg Ala Gln 745 1750 1755 1760
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- Asn Lys Leu Asp Asp Ala Trp Asp Leu Leu Arg Glu Ala Thr Asp Lys 1780 1785 1790
- Thr Arg Asp Ala Asn Arg Leu Ser Ala Ala Asn Gln Lys Asn Met Thr 1795 1800 1805
- Ile Leu Glu Thr Lys Lys Glu Ala Ile Glu Gly Ser Lys Arg Gln Ile 1810 1815 1820
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825 1830 1835 1840

- Leu Leu Gly Glu Ile Asn Ser Val Ile Asp Tyr Val Asp Asp Ile Lys 1845 1850 1855
- Thr Lys Leu Pro Pro Met Ser Glu Glu Leu Ser Asp Lys Ile Asp Asp 1860 1865 1870
- Leu Ala Gln Glu Ile Lys Asp Arg Arg Leu Ala Glu Lys Val Phe Gln 1875 1880 1885
- Ala Glu Ser His Ala Ala Gln Leu Asn Asp Ser Ser Ala Val Leu Asp 1890 1895 1900
- Gly Ile Leu Asp Glu Ala Lys Asn Ile Ser Phe Asn Ala Thr Ala Ala 905 1910 1915 1920
- Phe Arg Ala Tyr Ser Asn Ile Lys Asp Tyr Ile Asp Glu Ala Glu Lys 1925 1930 1935
- Val Ala Arg Glu Ala Lys Glu Leu Ala Gln Gly Ala Thr Lys Leu Ala 1940 1945 1950
- Thr Ser Pro Gln Gly Leu Leu Lys Glu Asp Ala Lys Gly Ser Leu Gln 1955 1960 1965
- Lys Ser Phe Arg Ile Leu Asn Glu Ala Lys Lys Leu Ala Asn Asp Val 1970 1975 1980
- Lys Gly Asn His Asn Asp Leu Asn Asp Leu Lys Thr Arg Leu Glu Thr 985 1990 1995 2000
- Ala Asp Leu Arg Asn Ser Gly Leu Leu Gly Ala Leu Asn Asp Thr Met 2005 2010 2015
- Asp Lys Leu Ser Ala Ile Thr Asn Asp Thr Ala Ala Lys Leu Gln Ala 2020 2025 2030
- Val Lys Glu Lys Ala Arg Glu Ala Asn Asp Thr Ala Lys Ala Val Leu 2035 2040 2045
- Ala Gln Val Lys Asp Leu His Gln Asn Leu Asp Gly Leu Lys Gln Asn 2050 2055 2060
- Tyr Asn Lys Leu Ala Asp Ser Val Ala Lys Thr Asn Ala Val Val Lys 065 2070 2075 2080
- Asp Pro Ser Lys Asn Lys Ile Ile Ala Asp Ala Gly Thr Ser Val Arg 2085 2090 2095
- Asn Leu Glu Glu Ala Asp Arg Leu Ile Asp Lys Leu Lys Pro Ile 2100 2105 2110
- Lys Glu Leu Glu Asp Asn Leu Lys Lys Asn Ile Ser Glu Ile Lys Glu 2115 2120 2125
- Leu Ile Asn Gln Ala Arg Lys Gln Ala Asn Ser Ile Lys Val Ser Val 2130 2135 2140
- Ser Ser Gly Gly Asp Cys Val Arg Thr Tyr Arg Pro Glu Ile Lys Lys 145 2150 2155 2160

Gly Ser Tyr Asn Asn Ile Val Val His Val Lys Thr Ala Val Ala Asp 2165 2170 2175

- Asn Leu Leu Phe Tyr Leu Gly Ser Ala Lys Phe Ile Asp Phe Leu Ala 2180 2185 2190
- Ile Glu Met Arg Lys Gly Lys Val Ser Phe Leu Trp Ile Val Gly Ser 2195 2200 2205
- Gly Val Gly Arg Val Gly Phe Pro Asp Leu Thr Ile Asp Asp Ser Tyr 2210 2215 2220
- Trp Tyr Arg Ile Glu Ala Ser Arg Thr Gly Arg Asn Gly Ser Ile Ser 225 2230 2235 2240
- Val Arg Ala Leu Asp Gly Pro Lys Ala Ser Met Val Pro Ser Thr Tyr 2245 2250 2255
- His Ser Val Ser Pro Pro Gly Tyr Thr Ile Leu Asp Val Asp Ala Asn 2260 2265 2270
- Ala Met Leu Phe Val Gly Gly Leu Thr Gly Lys Ile Lys Lys Ala Asp 2275 2280 2285
- Ala Val Arg Val Ile Thr Phe Thr Gly Cys Met Gly Glu Thr Tyr Phe 2290 2295 2300
- Asp Asn Lys Pro Ile Gly Leu Trp Asn Phe Arg Glu Lys Glu Gly Asp 305 2310 2315 2320
- Cys Lys Gly Cys Thr Val Ser Pro Gln Val Glu Asp Ser Glu Gly Thr 2325 2330 2335
- Ile Gln Phe Asp Gly Glu Gly Tyr Ala Leu Val Ser Arg Pro Ile Arg 2340 2345 2350
- Trp Tyr Pro Asn Ile Ser Thr Val Met Phe Lys Phe Arg Thr Phe Ser 2355 2360 2365
- Ser Ser Ala Leu Leu Met Tyr Leu Ala Thr Arg Asp Leu Lys Asp Phe 2370 2375 2380
- Met Ser Val Glu Leu Ser Asp Gly His Val Lys Val Ser Tyr Asp Leu 385 2390 2395 2400
- Gly Ser Gly Met Thr Ser Val Val Ser Asn Gln Asn His Asn Asp Gly 2405 2410 2415
- Lys Trp Lys Ala Phe Thr Leu Ser Arg Ile Gln Lys Gln Ala Asn Ile 2420 2425 2430
- Ser Ile Val Asp Ile Asp Ser Asn Gln Glu Glu Asn Val Ala Thr Ser  $2435 \hspace{1.5cm} 2440 \hspace{1.5cm} 2445$
- Ser Ser Gly Asn Asn Phe Gly Leu Asp Leu Lys Ala Asp Asp Lys Ile 2450 2455 2460
- Tyr Phe Gly Gly Leu Pro Thr Leu Arg Asn Leu Ser Met Lys Ala Arg 465 2470 2475 2480

Pro Glu Val Asn Val Lys Lys Tyr Ser Gly Cys Leu Lys Asp Ile Glu 2485 2490 2495

- Ile Ser Arg Thr Pro Tyr Asn Ile Leu Ser Ser Pro Asp Tyr Val Gly 2500 2505 2510
- Val Thr Lys Gly Cys Ser Leu Glu Asn Val Asn Thr Val Ser Phe Pro 2515 2520 2525
- Lys Pro Gly Phe Val Glu Leu Ala Ala Val Ser Ile Asp Val Gly Thr 2530 2540
- Glu Ile Asn Leu Ser Phe Ser Thr Arg Asn Glu Ser Gly Ile Ile Leu 545 2550 2565 2560
- Leu Gly Ser Gly Gly Thr Leu Thr Pro Pro Arg Arg Lys Arg Arg Gln 2565 2570 2575
- Thr Thr Gln Ala Tyr Tyr Ala Ile Phe Leu Asn Lys Gly Arg Leu Glu 2580 2585 2590
- Val His Leu Ser Ser Gly Thr Arg Thr Met Arg Lys Ile Val Ile Lys 2595 2600 2605
- Pro Glu Pro Asn Leu Phe His Asp Gly Arg Glu His Ser Val His Val 2610 2615 2620
- Glu Arg Thr Arg Gly Ile Phe Thr Val Gln Ile Asp Glu Asp Arg Arg 625 2630 2635 2640
- His Ile Gln Asn Leu Thr Glu Glu Gln Pro Ile Glu Val Lys Lys Leu 2645 2650 2655
- Phe Val Gly Gly Ala Pro Pro Glu Phe Gln Pro Ser Pro Leu Arg Asn 2660 2665 2670
- Ile Pro Ala Phe Gln Gly Cys Val Trp Asn Leu Val Ile Asn Ser Ile 2675 2680 2685
- Pro Met Asp Phe Ala Gln Pro Ile Ala Phe Lys Asn Ala Asp Ile Gly 2690 2695 2700
- Arg Cys Thr Tyr Gln Lys Pro Arg Glu Asp Glu Ser Glu Ala Val Pro 705 2710 2715 2720
- Ala Glu Val Ile Val Gln Pro Gln Ser Val Pro Thr Pro Ala Phe Pro 2725 2730 2735
- Phe Pro Val Pro Thr Met Val His Gly Pro Cys Val Ala Glu Ser Glu 2740 2745 2750
- Pro Ala Leu Leu Thr Gly Ser Lys Gln Phe Gly Leu Ser Arg Asn Ser 2755 2760 2765
- His Ile Ala Ile Val Phe Asp Asp Thr Lys Val Lys Asn Arg Leu Thr 2770 2775 2780
- Ile Glu Leu Glu Val Arg Thr Glu Ala Glu Ser Gly Leu Leu Phe Tyr 785 2790 2795 2800
- Met Gly Arg Ile Asn His Ala Asp Phe Gly Thr Val Gln Leu Arg Asn

2805 2810 2815

Gly Phe Pro Phe Phe Ser Tyr Asp Leu Gly Ser Gly Ser Thr Arg Thr 2820 2825 2830

- Met Ile Pro Thr Lys Ile Asn Asp Gly Gln Trp His Lys Ile Lys Ile 2835 2840 2845
- Val Arg Val Lys Gln Glu Gly Ile Leu Tyr Val Asp Asp Ala Ser Ser 2850 2855 2860
- Gln Thr Ile Ser Pro Lys Lys Ala Asp Ile Leu Asp Val Gly Gly Ile 865 2870 2875 2880
- Leu Tyr Val Gly Gly Leu Pro Ile Asn Tyr Thr Thr Arg Arg Ile Gly 2885 2890 2895
- Pro Val Thr Tyr Ser Leu Asp Gly Cys Val Arg Asn Leu His Met Glu 2900 2905 2910
- Gln Ala Pro Val Asp Leu Asp Gln Pro Thr Ser Ser Phe His Val Gly 2915 2920 2925
- Thr Cys Phe Ala Asn Ala Glu Ser Gly Thr Tyr Phe Asp Gly Thr Gly 2930 2935 2940
- Phe Gly Lys Ala Val Gly Gly Phe Ile Val Gly Leu Asp Leu Leu Val 945 2950 2955 2960
- Glu Phe Glu Phe Arg Thr Thr Arg Pro Thr Gly Val Leu Leu Gly Ile 2965 2970 2975
- Ser Ser Gln Lys Met Asp Gly Met Gly Ile Glu Met Ile Asp Glu Lys 2980 2985 2990
- Leu Met Phe His Val Asp Asn Gly Ala Gly Arg Phe Thr Ala Ile Tyr 2995 3000 3005
- Asp Ala Glu Ile Pro Gly His Met Cys Asn Gly Gln Trp Tyr Lys Val
- Thr Ala Lys Lys Ile Lys Asn Arg Leu Glu Leu Val Val Asp Gly Asn 025 3030 3035 3040
- Gln Val Asp Ala Gln Ser Pro Asn Ser Ala Ser Thr Ser Ala Asp Thr 3045 3050 3055
- Asn Asp Pro Val Phe Val Gly Gly Phe Pro Gly Gly Leu Asn Gln Phe 3060 3065 3070
- Gly Leu Thr Thr Asn Ile Arg Phe Arg Gly Cys Ile Arg Ser Leu Lys 3075 3080 3085
- Leu Thr Lys Gly Thr Ala Asn Arg Trp Arg Leu Ile Leu Pro Arg Pro 3090 3095 3100

Trp Asn 105

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gtc Val	ctg Leu	aat Asn	ctt Leu 20	gct Ala	tcg Ser	aat Asn	gca Ala	ctc Leu 25	atc Ile	aca Thr	acc Thr	aat Asn	gct Ala 30	aca Thr	tgt Cys	96
		aaa Lys 35														144
		cct Pro														192
		cca Pro														240
		tgg Trp														288
		aca Thr														336
		gtg Val 115														384
		tcc Ser														432
		gac Asp														480
		cca Pro														528
		aag Lys														576
		999 Gly 195														624

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ttg Leu 225	aat Asn	gca Ala	gac Asp	ttg Leu	atg Met 230	atg Met	ttt Phe	gct Ala	cac Kis	aaa Lys 235	gac Asp	ccc Pro	aga Arg	gaa Glu	atc Ile 240	720
gat Asp	ccc Pro	att Ile	gtc Val	aca Thr 245	cga Arg	aga Arg	tat Tyr	tac Tyr	tat Tyr 250	tct Ser	gtc Val	aag Lys	gat Asp	att Ile 255	tca Ser	768
gtt Val	ggc Gly	Gly ggg	atg Met 260	tgc Cys	atc Ile	tgt Cys	tat Tyr	ggt Gly 265	cat His	gcc Ala	cgg Arg	gct Ala	tgt Cys 270	cca Pro	ctt Leu	816
			aca Thr													864
			tgt Cys													912
			acc Thr													960
			gct Ala													1008
			tta Leu 340													1056
			aca Thr													1104
			ttc Phe													1152
tgc Cys 385	cag Gln	cca Pro	tgt Cys	cac His	tgt Cys 390	gat Asp	cca Pro	act Thr	ggc Gly	tcc Ser 395	ctt Leu	agt Ser	gaa Glu	gtc Val	tgt Cys 400	1200
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			act Thr 420													1296
			ggt Gly													1344
999	agc	aca	aat	gag	gac	cct	tgc	gtt	999	ccc	tgt	agc	tgt	aag	gag	1392

Gly	Ser 450	Thr	Asn	Glu	Asp	Pro 455	Сув	Val	Gly	Pro	Сув 460	Ser	Сув	Lys	Glu	
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			ggt Gly													1584
			ctt Leu													1632
			gcc Ala													1680
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aga																

690		695	•	700	
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ggc acc att Gly Thr Ile	ttt ggt ggc Phe Gly Gly 725	att tgt gaa Ile Cys Glu	cca tgt ( Pro Cys ( 730	cag tgc ttt Gln Cys Phe	gct cat 2208 Ala His 735
	tgt gat gac Cys Asp Asp 740				
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tgc Cys	cag Gln	cct Pro	gga Gly	gta Val 965	gca Ala	Gly ggg	aag Lys	aaa Lys	tgt Cys 970	gac Asp	cgt Arg	tgt Cys	gcc Ala	cat His 975	ggc Gly	2928
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						Pro					Сув			cca Pro		3024
Asn					Lys					Leu				tgg Trp		3072
cac His 1025	Ser	att Ile	gtc Val	Thr	ggc Gly L030	tgt Cys	aag Lys	gtt Val	Сув	aac Asn 1035	tgc Cys	agc Ser	act Thr	gtg Val	999 Gly 1040	3120
			Ser					Asn					Ser	tgt Cys 1055		3168
cca Pro	aaa Lys	Phe	tct Ser 1060	ggt Gly	atg Met	aaa Lys	Сув	tca Ser 1065	gag Glu	tgc Cys	agc Ser	Arg	ggt Gly L070	cac His	tgg Trp	3216
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Āla					Leu					Cys				gat Asp		3312
	Gly			Ser					Val					tgt Cys 1		3360
			Pro					Leu					Pro	ctt Leu 135		3408
		Ser					Gly					Суя		gaa Glu		3456
	Gly					Trp					Asp			acc Thr		3504
Leu					Glu					Thr				ggc Gly		3552

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c tgt gaa agg tgt gcc cca ggc tat act 4 r Cys Glu Arg Cys Ala Pro Gly Tyr Thr 1480 1485	Ala Pro Gly T 1485	Сув	Arg	Glu	Сув 1480	Tyr	Gln	Gly	Glu	Tyr 1475	Gly	Arg
	31u Cys Glu C 500	Gln 1	Сув	Ser	Gly	Gly 1495	Pro	Ser	Ser	Pro	Ser 1490	Gly
t ccc tgt gac cgg gtc aca gga ctc tgc 4 l Pro Cys Asp Arg Val Thr Gly Leu Cys 1515 1520	Val Thr Gly L	Arg 1515	Asp	Сув	Pro	Val	Pro 1510	Leu	Ser	Gly	Tyr 5	Pro 150
a gga agg aag tgt gat ggc tgc gag cac 4 r Gly Arg Lys Cys Asp Gly Cys Glu His 1530 1535	Asp Gly Cys G 15	Cys .	Lys 1530	Arg	Gly	Thr	Ala	Gly 1525	Pro	Arg	Cys	Thr
a gag tgt gtc ttt tgt gga gac gag tgt 4 a Glu Cys Val Phe Cys Gly Asp Glu Cys 1545 1550	Cys Gly Asp G 1550	Phe	Val	Сув 1545	Glu	Ala	Gly	Glu	Arg 1540	Ala	His	Trp
c ctg gct cgt cta gag cag atg acc atg 4 p Leu Ala Arg Leu Glu Gln Met Thr Met 1560 1565	Glu Gln Met Ti 1565	Leu	Arg	Āla	Leu 1560	Asp	Gly	Leu	Leu	Leu 1555	Gly	Thr
	Tyr Lys Ile L 580	Pro	Āla	Pro	Leu	Pro 1575	Gly	Thr	Leu	Asn	Ile 1570	Asn
g gaa ctc aag cac ctg cta tca ccg caa 4 n Glu Leu Lys His Leu Leu Ser Pro Gln 1595 1600	beu Leu Ser P	His : 1595	Lys :	Leu	Glu	Gln	Thr 1590	Thr	Asn	Glu	Leu 5	Gly 158!
t cag ttg gca gag ggc aac gtg aac aca 4 e Gln Leu Ala Glu Gly Asn Val Asn Thr 1610 1615	Gly Asn Val As 16:	Glu (	Ala 1610	Leu	Gln	Ile	Leu	Arg 1605	Glu	Pro	Ala	Arg
g ctg cta acc aga gca acc aaa gtg aca 4 1 Leu Leu Thr Arg Ala Thr Lys Val Thr 1625 1630	Ala Thr Lys Va 1630	Arg i	Thr	Leu 1625	Leu	Glu	Asn	Thr	Glu 1620	Met	Val	Leu
a caa gat get gag agg acc aac tee aga 4 y Gln Asp Ala Glu Arg Thr Asn Ser Arg 1640 1645	Arg Thr Asn Se 1645	Glu i	Ala	Asp	Gln 1640	Gly	Thr	Gln	Glu	Gly 1635	Asp	Ala
	Val Gln Asp A 1660	Leu 1	Gly	Lys	Ile	Phe 1655	Glu	Glu	Leu	Ser	Glu 1650	Ala :
a aaa cta aat gaa acc tta gga aat caa 5 l Lys Leu Asn Glu Thr Leu Gly Asn Gln	icc tta gga aa Thr Leu Gly As	gaa a Glu :	aat Asn	cta Leu	aaa Lys	gta Val	gct Ala	aaa Lys	gaa Glu	aat Asn	ata Ile	gcc Ala

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	Gly Ser Lys A		ac act tta aag gaa sn Thr Leu Lys Glu 1805	5424
			ta ggt gaa atc aac eu Gly Glu Ile Asn 20	5472
			ag ttg cca cca atg ys Leu Pro Pro Met 1840	5520
Ser Glu Glu Leu			cc cag gaa ata aag la Gln Glu Ile Lys 1855	5568
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			ga gct tac agt aat rg Ala Tyr Ser Asn 00	5712
			cc aga gaa gcc aaa la Arg Glu Ala Lys 1920	5760

gag ctt gcc Glu Leu Ala		Thr Lys Leu			
tta aaa gaa Leu Lys Glu 1					
aat gaa gcc Asn Glu Ala 1955			Val Lys Gly		
cta aat gac Leu Asn Asp 1970	Leu Lys Thr				
gga ctt cta Gly Leu Leu 1985				Leu Ser Ala	
aca aat gac Thr Asn Asp		Lys Leu Gln			
gaa gcc aat Glu Ala Asn 2					
cat cag aac His Gln Asn 2035			Asn Tyr Asn		
agc gtg gcc Ser Val Ala 2050	Lys Thr Asn				
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gac cgg cta Asp Arg Leu		Leu Lys Pro			
cta aag aaa Leu Lys Lys . 2					
aaa caa gct Lys Gln Ala 2115			Val Ser Ser		
gtt cgg aca Val Arg Thr 2130	Tyr Arg Pro				

gga agt Gly Ser	gcc Ala	Lys	ttt Phe 2165	att Ile	gac Asp	ttt Phe	Leu	gct Ala 2170	ata Ile	gaa Glu	atg Met	Arg	aaa Lys 2175	ggc	6528
aaa gtc Lys Val	Ser	ttc Phe 2180	ctc Leu	tgg Trp	att Ile	Val	ggc Gly 2185	tct Ser	gga Gly	gtt Val	Gly	cga Arg 2190	gta Val	gjå aaa	6576
ttt cca Phe Pro	gac Asp 2195	ttg Leu	acc Thr	atc Ile	qaA	gac Asp 200	tcc Ser	tat Tyr	tgg Trp	Tyr	cgt Arg 2205	att Ile	gaa Glu	gca Ala	6624
tca aga Ser Arg 2210	Thr	gga Gly	aga Arg	Asn	gga Gly 2215	tct Ser	att Ile	tct Ser	Val	aga Arg 2220	gct Ala	tta Leu	gat Asp	gga Gly	6672
ccc aaa Pro Lys 2225			Met					Tyr					Pro		6720
ggg tat Gly Tyr		Ile					Ala					Phe			6768
ggc ctg Gly Leu	Thr					Lys					Arg				6816
ttc acc Phe Thr					Ğlu					Asn					6864
tta tgg Leu Trp 2290	Asn			Glu					Cys						6912
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tat ctt Tyr Leu															7104
	2355					360					365				
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Asp Gly	2355 cat His	gtg Val aat	aaa Lys caa Gln	gtc Val 2	agc Ser 2375 cat	tat Tyr aat	gac Asp gat	ctg Leu 999 Gly	ggc Gly 2	tca Ser 380 tgg	99a Gly aaa	atg Met gca	Thr ttc Phe	Ser	7152 7200

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ggt Gly	Leu	gac Asp 2435	ttg Leu	aaa Lys	gca Ala	qaA	gac Asp 2440	aaa Lys	ata Ile	tat Tyr	Phe	ggt Gly 2445	ggc	ctg Leu	cca Pro	7344
Thr	ctg Leu !450	aga Arg	aac Asn	ttg Leu	Ser	atg Met 2455	aaa Lys	gca Ala	agg Arg	Pro	gaa Glu 2460	gtc Val	aat Asn	gtg Val	aag Lys	7392
	Tyr			Сув					Glu					cct Pro		7440
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ctg Leu	gag Glu	Asn	gtt Val 500	aat Asn	aca Thr	gtt Val	Ser	ttc Phe 2505	ccc Pro	aag Lys	cct Pro	Gly	ttt Phe 510	gtg Val	gag Glu	7536
ctt Leu	Ala	gct Ala 515	gtg Val	tct Ser	att Ile	qaA	gtt Val 2520	gga Gly	aca Thr	gaa Glu	Ile	aat Asn 2525	ctg Leu	tcc Ser	ttt Phe	7584
Ser					Ser					Leu				gjy aaa		7632
	Thr			Arg					Gln					tat Tyr 2		7680
			Leu					Leu					Ser	tcg Ser 2575		7728
		Thr					Val					Pro		ttg Leu		7776
	qeA					Ser					Arg			ggc Gly		7824
Phe					Asp					His				ctg Leu		7872
	Glu			Ile					Leu					gct Ala 2		7920
														caa Gln		7968

2645 2650 2655 tgt gtg tgg aac ctt gtt att aac tcc atc ccc atg gac ttt gcg cag 8016 Cys Val Trp Asn Leu Val Ile Asn Ser Ile Pro Met Asp Phe Ala Gln cct ata gcc ttc aaa aat gcc gac att ggt cgc tgt acc tat caa aag Pro Ile Ala Phe Lys Asn Ala Asp Ile Gly Arg Cys Thr Tyr Gln Lys 8064 ccc cgg gaa gat gag agt gaa gca gtt cca gct gaa gtt att gtc cag Pro Arg Glu Asp Glu Ser Glu Ala Val Pro Ala Glu Val Ile Val Gln 8112 2695 cct cag tcg gtg ccc acc cct gcc ttc cct ttc cca gtc ccc acc atg Pro Gln Ser Val Pro Thr Pro Ala Phe Pro Phe Pro Val Pro Thr Met 8160 gtg cat ggc cct tgt gtt gca gaa tca gaa cca gct ctt ctg aca ggg Val His Gly Pro Cys Val Ala Glu Ser Glu Pro Ala Leu Leu Thr Gly 8208 2730 age aag cag tit ggg ett tee aga aac age cae att gea att gte tit 8256 Ser Lys Gln Phe Gly Leu Ser Arg Asn Ser His Ile Ala Ile Val Phe 2745 gat gac acc aaa gtt aaa aac cgc ctc acc att gag ctg gag gta cga Asp Asp Thr Lys Val Lys Asn Arg Leu Thr Ile Glu Leu Glu Val Arg act gaa gct gaa tca ggc ttg ctc ttc tac atg ggt cgg atc aat cat Thr Glu Ala Glu Ser Gly Leu Leu Phe Tyr Met Gly Arg Ile Asn His gct gat ttt ggt act gtt cag ctg agg aat ggg ttc ccg ttc ttc agt Ala Asp Phe Gly Thr Val Gln Leu Arg Asn Gly Phe Pro Phe Phe Ser tat gat ttg ggg agt ggg agc acc aga acc atg atc ccc aca aaa atc Tyr Asp Leu Gly Ser Gly Ser Thr Arg Thr Met Ile Pro Thr Lys Ile aac gat ggt cag tgg cac aag att aag att gtg aga gtg aag cag gag Asn Asp Gly Gln Trp His Lys Ile Lys Ile Val Arg Val Lys Gln Glu 8496 gga att ctt tat gtg gat gat gcc tcc agc caa acc atc agt ccc aag Gly Ile Leu Tyr Val Asp Asp Ala Ser Ser Gln Thr Ile Ser Pro Lys 8544 aaa gcc gac atc ctg gat gtc ggg ggg att ctg tat gtc ggt gga ttg Lys Ala Asp Ile Leu Asp Val Gly Gly Ile Leu Tyr Val Gly Gly Leu 8592 8640 gat ggc tgt gtt agg aat ctt cac atg gaa caa gcc cct gtt gat ctg Asp Gly Cys Val Arg Asn Leu His Met Glu Gln Ala Pro Val Asp Leu 8688 2890

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ggg ttc a Gly Phe I 2930	tc gtt le Val	Gly Leu	gac ctt Asp Leu 1935	ctt Leu	gtg Val	Glu	ttt Phe 940	gaa Glu	ttc Phe	cgt Arg	acc Thr	8832
aca aga co Thr Arg P: 2945					Ile					Met		8880
gga atg g Gly Met G	ly Ile			Glu					His			8928
aat ggc g Asn Gly A			Thr Ala					Glu				8976
cac atg to His Met C	ys Asn						Ala					9024
aac cgt c Asn Arg L 3010		Leu Val				Gln						9072
cca aac t Pro Asn S 3025					Thr .					Phe		9120
ggc ggt t Gly Gly P	he Pro			Gln					Thr			9168
agg ttc c Arg Phe A			Arg Ser					Lys				9216
aac cgc t Asn Arg T	rp Arg							tgag	gggt	gt.		9262
tcaacctgt	a tcatg	jecega et	acctaat	a aag	atag	ttc	aatc	ctga	gg a	gaat	tcatc	9322
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Gly	Glu	Lys 35	Gly	Pro	Glu	Met	Tyr 40	Сув	Lys	Leu	Val	Glu 45	His	Val	Pro
Gly	Gln 50	Pro	Val	Arg	Asn	Pro 55	Gln	Сув	Arg	Ile	Сув 60	Asn	Gln	naA	Ser
Ser 65	Asn	Pro	Tyr	Gln	Arg 70	His	Pro	Ile	Thr	Asn 75	Ala	Ile	Авр	Gly	Lys 80
neA	Thr	Trp	Trp	Gln 85	Ser	Pro	Ser	Ile	90 Lys	Asn	Gly	Val	Glu	Tyr 95	His
Tyr	Val	Thr	11e 100	Thr	Leu	Asp	Leu	Gln 105	Gln	Val	Phe	Gln	Ile 110	Ala	Tyr
Val	Ile	Val 115	Lys	Ala	Ala	Asn	Ser 120	Pro	Arg	Pro	Gly	Asn 125	Trp	Ile	Leu
Glu	Arg 130	Ser	Leu	Asp	qaA	Val 135	Glu	Tyr	Lys	Pro	Trp 140	Gln	Tyr	His	Ala
Val 145	Thr	Asp	Thr	Glu	Сув 150	Leu	Thr	Leu	Tyr	Asn 155	Ile	Tyr	Pro	Arg	Thr 160
Gly	Pro	Pro	Ser	Tyr 165	Ala	Lys	Asp	Asp	Glu 170	Val	Ile	Cys	Thr	Ser 175	Phe
Tyr	Ser	Lys	Ile 180	His	Pro	Leu	Glu	Asn 185	Gly	Glu	Ile	His	11e 190	Ser	Leu
Ile	Asn	Gly 195	Arg	Pro	Ser	Ala	Asp 200	Asp	Pro	Ser	Pro	Glu 205	Leu	Leu	Glu
Phe	Thr 210	Ser	Ala	Arg	Tyr	11e 215	Arg	Leu	Arg	Phe	Gln 220	Arg	Ile	Arg	Thr
Leu 225	Asn	Ala	Asp	Leu	Met 230	Met	Phe	Ala	His	Lys 235	qaA	Pro	Arg	Glu	Ile 240
Asp	Pro	Ile	Val	Thr 245	Arg	Arg	Tyr	Tyr	Tyr 250	Ser	Val	Lys	Asp	Ile 255	Ser
Val	Gly	Gly	Met 260	Сув	Ile	Суз	Tyr	Gly 265	His	Ala	Arg	Ala	Суs 270	Pro	Leu
Авр	Pro	Ala 275	Thr	Asn	Lys	ser	Arg 280	Сув	Glu	Сув	Glu	His 285	Asn	Thr	Сув
Gly	Glu 290	Ser	Сла	Asp	Arg	Сув 295	Сув	Pro	Gly	Phe	His 300	Gln	ГÀЗ	Pro	Trp
Arg 305	Ala	Gly	Thr	Phe	Leu 310	Thr	Lys	Ser	Glu	Cys 315	Glu	Ala	Cys	Asn	Cys 320

His Gly Lys Ala Glu Glu Cys Tyr Tyr Asp Glu Thr Val Ala Ser Arg 325 330 335

- Asn Leu Ser Leu Asn Ile His Gly Lys Tyr Ile Gly Gly Val Cys 340 345 350
- Ile Asn Cys Thr His Asn Thr Ala Gly Ile Asn Cys Glu Thr Cys Val
- Asp Gly Phe Phe Arg Pro Lys Gly Val Ser Pro Asn Tyr Pro Arg Pro 370 375 380
- Cys Gln Pro Cys His Cys Asp Pro Thr Gly Ser Leu Ser Glu Val Cys 385 390 395 400
- Val Lys Asp Glu Lys Tyr Ala Gln Arg Gly Leu Lys Pro Gly Ser Cys 405 410 415
- His Cys Lys Thr Gly Phe Gly Gly Val Asn Cys Asp Arg Cys Val Arg 420 425 430 .
- Gly Tyr His Gly Tyr Pro Asp Cys Gln Pro Cys Asn Cys Ser Gly Leu 435 440 445
- Gly Ser Thr Asn Glu Asp Pro Cys Val Gly Pro Cys Ser Cys Lys Glu 450 455 460
- Asn Val Glu Gly Glu Asp Cys Ser Arg Cys Lys Ser Gly Phe Phe Asn 465 470 475 480
- Leu Gln Glu Asp Asn Gln Lys Gly Cys Glu Glu Cys Phe Cys Ser Gly 485 490 495
- Val Ser Asn Arg Cys Gln Ser Ser Tyr Trp Thr Tyr Gly Asn Ile Gln 500 505 510
- Asp Met Arg Gly Trp Tyr Leu Thr Asp Leu Ser Gly Arg Ile Arg Met 515 520 525
- Ala Pro Gln Leu Asp Asn Pro Asp Ser Pro Gln Gln Ile Ser Ile Ser 530 540
- Asn Ser Glu Ala Arg Lys Ser Leu Leu Asp Gly Tyr Tyr Trp Ser Ala 545 550 555 560
- Pro Pro Pro Tyr Leu Gly Asn Arg Leu Pro Ala Val Gly Gly Gln Leu
  565 570 575
- Ser Phe Thr Ile Ser Tyr Asp Leu Glu Glu Glu Glu Asp Asp Thr Glu 580 595
- Lys Leu Leu Gln Leu Met Ile Ile Phe Glu Gly Asn Asp Leu Arg Ile 595 600 605
- Ser Thr Ala Tyr Lys Glu Val Tyr Leu Glu Pro Ser Glu Glu His Val 610 615 620
- Glu Glu Val Ser Leu Lys Glu Glu Ala Phe Thr Ile His Gly Thr Asn 625 630 635 640
- Leu Pro Val Thr Arg Lys Asp Phe Met Ile Val Leu Thr Asn Leu Gly

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Arg	Leu	Ser 675	Ser	Val	Asn	Leu	Glu 680	Ser	Pro	Val	Pro	Tyr 685	Pro	Thr	Asp
	690		Ala			695					700				
Ser 705	Gly	Ser	Ser	Cys	Glu 710	Thr	Сув	Trp	Pro	Arg 715	His	Arg	Arg	Val	Авл 720
Gly	Thr	Ile	Phe	Gly 725	Gly	Ile	Сув	Glu	Pro 730	Сув	Gln	Сув	Phe	Ala 735	His
			Сув 740					745					750		
His	Thr	Gly 755	Gly	Pro	Tyr	Сув	Asn 760	Glu	Cys	Leu	Pro	Gly 765	Phe	Tyr	Gly
Asp	Pro 770	Thr	Arg	Gly	Ser	Pro 775	Glu	Ąsp	Сув	Gln	Pro 780	Сув	Ala	Cys	Pro
Leu 785	Asn	Ile	Pro	Ser	Asn 790	Asn	Phe	Ser	Pro	Thr 795	Сув	His	Leu	Asp	Arg 800
Ser	Leu	Gly	Leu	Ile 805	Сув	Asp	Glu	Сув	Pro 810	Ile	Gly	Tyr	Thr	Gly 815	Pro
			Arg 820					825					830		
		835	Сув				840					845			
	850		Ser			855					860			-	-
865			Thr		870					875		_	_	•	880
			Val	885					890					895	
			Phe 900					905					910		
		915	Asn				920					925			
	930		Leu			935					940				
945			Ser		950					955					960
Cys	Gln	Pro	Gly	Val 965	Ala	Gly	Lys	Lys	Cys 970	Asp	Arg	Cys	Ala	His 975	Gly

Tyr Phe Asn Phe Gln Glu Gly Gly Cys Ile Ala Cys Asp Cys Ser His 980 985 990

- Leu Gly Asn Asn Cys Asp Pro Lys Thr Gly Gln Cys Ile Cys Pro Pro 995 1000 1005
- Asn Thr Thr Gly Glu Lys Cys Ser Glu Cys Leu Pro Asn Thr Trp Gly 1010 1015 1020
- His Ser Ile Val Thr Gly Cys Lys Val Cys Asn Cys Ser Thr Val Gly 1025 1030 1035 1040
- Ser Leu Ala Ser Gln Cys Asn Val Asn Thr Gly Gln Cys Ser Cys His 1045 1050 1055
- Pro Lys Phe Ser Gly Met Lys Cys Ser Glu Cys Ser Arg Gly His Trp 1060 1065 1070
- Asn Tyr Pro Leu Cys Thr Leu Cys Asp Cys Phe Leu Pro Gly Thr Asp 1075 1080 1085
- Ala Thr Thr Cys Asp Leu Glu Thr Arg Lys Cys Ser Cys Ser Asp Gln 1090 1095 1100
- Thr Gly Gln Cys Ser Cys Lys Val Asn Val Glu Gly Val His Cys Asp 1105 1110 1115 1120
- Arg Cys Arg Pro Gly Lys Phe Gly Leu Asp Ala Lys Asn Pro Leu Gly 1125 1130 1135
- Cys Ser Ser Cys Tyr Cys Phe Gly Val Thr Ser Gln Cys Ser Glu Ala 1140 1145 1150
- Lys Gly Leu Ile Arg Thr Trp Val Thr Leu Ser Asp Glu Gln Thr Ile 1155 1160 1165
- Leu Pro Leu Val Asp Glu Ala Leu Gln His Thr Thr Thr Lys Gly Ile 1170 1175 1180
- Ala Phe Gln Lys Pro Glu Ile Val Ala Lys Met Asp Glu Val Arg Gln 1185 1190 1195 1200
- Glu Leu His Leu Glu Pro Phe Tyr Trp Lys Leu Pro Gln Gln Phe Glu 1205 1210 1215
- Gly Lys Lys Leu Met Ala Tyr Gly Gly Lys Leu Lys Tyr Ala Ile Tyr 1220 1225 1230
- Phe Glu Ala Arg Asp Glu Thr Gly Phe Ala Thr Tyr Lys Pro Gln Val 1235 1240 1245
- Ile Ile Arg Gly Gly Thr Pro Thr His Ala Arg Ile Ile Thr Arg His
- Met Ala Ala Pro Leu Ile Gly Gln Leu Thr Arg His Glu Ile Glu Met 1265 1270 1275 1280
- Thr Glu Lys Glu Trp Lys Tyr Tyr Gly Asp Asp Pro Arg Ile Ser Arg 1285 1290 1295

Thr Val Thr Arg Glu Asp Phe Leu Asp Ile Leu Tyr Asp Ile His Tyr 1300 1305 1310

- Ile Leu Ile Lys Ala Thr Tyr Gly Asn Val Val Arg Gln Ser Arg Ile 1315 1320 1325
- Ser Glu Ile Ser Met Glu Val Ala Glu Pro Gly His Val Leu Ala Gly 1330 1335 1340
- Ser Pro Pro Ala His Leu Ile Glu Arg Cys Asp Cys Pro Pro Gly Tyr 1345 1350 1355 1360
- Ser Gly Leu Ser Cys Glu Thr Cys Ala Pro Gly Phe Tyr Arg Leu Arg 1365 1370 1375
- Ser Glu Pro Gly Gly Arg Thr Pro Gly Pro Thr Leu Gly Thr Cys Val
- Pro Cys Gln Cys Asn Gly His Ser Ser Gln Cys Asp Pro Glu Thr Ser 1395 1400 1405
- Val Cys Gln Asn Cys Gln His His Thr Ala Gly Asp Phe Cys Glu Arg 1410 1415 1420
- Cys Ala Leu Gly Tyr Tyr Gly Ile Val Arg Gly Leu Pro Asn Asp Cys 1425 1430 1435 1440
- Gln Pro Cys Ala Cys Pro Leu Ile Ser Pro Ser Asn Asn Phe Ser Pro 1445 1450 1455
- Ser Cys Val Leu Glu Gly Leu Glu Asp Tyr Arg Cys Thr Ala Cys Pro 1460 1465 1470
- Arg Gly Tyr Glu Gly Gln Tyr Cys Glu Arg Cys Ala Pro Gly Tyr Thr \$1475\$ \$1480\$ \$1485
- Gly Ser Pro Ser Ser Pro Gly Gly Ser Cys Gln Glu Cys Glu Cys Asp 1490 1495 1500
- Pro Tyr Gly Ser Leu Pro Val Pro Cys Asp Arg Val Thr Gly Leu Cys 1505 1510 1515 1520
- Thr Cys Arg Pro Gly Ala Thr Gly Arg Lys Cys Asp Gly Cys Glu His 1525 1530 1535
- Trp His Ala Arg Glu Gly Ala Glu Cys Val Phe Cys Gly Asp Glu Cys 1540 1545 1550
- Thr Gly Leu Leu Gly Asp Leu Ala Arg Leu Glu Gln Met Thr Met 1555 1560 1565
- Asn Ile Asn Leu Thr Gly Pro Leu Pro Ala Pro Tyr Lys Ile Leu Tyr 1570 1575 1580
- Gly Leu Glu Asn Thr Thr Gln Glu Leu Lys His Leu Leu Ser Pro Gln 1585 1590 1595 1600
- Arg Ala Pro Glu Arg Leu Ile Gln Leu Ala Glu Gly Asn Val Asn Thr 1605 1610 1625
- Leu Val Met Glu Thr Asn Glu Leu Leu Thr Arg Ala Thr Lys Val Thr

1620 1625 1630

Ala Asp Gly Glu Gln Thr Gly Gln Asp Ala Glu Arg Thr Asn Ser Arg 1635 1640 1645

- Ala Glu Ser Leu Glu Glu Phe Ile Lys Gly Leu Val Gln Asp Ala Glu 1650 1655 1660
- Ala Ile Asn Glu Lys Ala Val Lys Leu Asn Glu Thr Leu Gly Asn Gln 1665 1670 1675 1680
- Asp Lys Thr Ala Glu Arg Asn Leu Glu Glu Leu Gln Lys Glu Ile Asp 1685 1690 1695
- Arg Met Leu Lys Glu Leu Arg Ser Lys Asp Leu Gln Thr Gln Lys Glu 1700 1705 1710
- Val Ala Glu Asp Glu Leu Val Ala Ala Glu Gly Leu Leu Lys Arg Val 1715 1720 1725
- Asn Lys Leu Phe Gly Glu Pro Arg Ala Gln Asn Glu Asp Met Glu Lys 1730 1735 1740
- Asp Leu Gln Gln Lys Leu Ala Glu Tyr Lys Asn Lys Leu Asp Asp Ala 1745 1750 1755 1760
- Trp Asp Leu Leu Arg Glu Ala Thr Asp Lys Thr Arg Asp Ala Asn Arg 1765 1770 1775
- Leu Ser Ala Ala Asn Gln Lys Asn Met Thr Ile Leu Glu Thr Lys Lys 1780 1785 1790
- Glu Ala Ile Glu Gly Ser Lys Arg Gln Ile Glu Asn Thr Leu Lys Glu 1795 1800 1805
- Gly Asn Asp Ile Leu Asp Glu Ala Asn Gln Leu Leu Gly Glu Ile Asn 1810 1815 1820
- Ser Val Ile Asp Tyr Val Asp Asp Ile Lys Thr Lys Leu Pro Pro Met 1825 1830 1835 1840
- Ser Glu Glu Leu Ser Asp Lys Ile Asp Asp Leu Ala Gln Glu Ile Lys 1845 1850 1855
- Asp Arg Arg Leu Ala Glu Lys Val Phe Gln Ala Glu Ser His Ala Ala 1860 1865 1870
- Gln Leu Asn Asp Ser Ser Ala Val Leu Asp Gly Ile Leu Asp Glu Ala 1875 1880 1885
- Lys Asn Ile Ser Phe Asn Ala Thr Ala Ala Phe Arg Ala Tyr Ser Asn 1890 1895 1900
- Ile Lys Asp Tyr Ile Asp Glu Ala Glu Lys Val Ala Arg Glu Ala Lys 1905 1910 1915 1920
- Glu Leu Ala Gln Gly Ala Thr Lys Leu Ala Thr Ser Pro Gln Gly Leu 1925 1930 1935
- Leu Lys Glu Asp Ala Lys Gly Ser Leu Gln Lys Ser Phe Arg Ile Leu 1940 1945 1950

Asn Glu Ala Lys Lys Leu Ala Asn Asp Val Lys Gly Asn His Asn Asp 1955 1960 1965

- Leu Asn Asp Leu Lys Thr Arg Leu Glu Thr Ala Asp Leu Arg Asn Ser 1970 1975 1980
- Gly Leu Leu Gly Ala Leu Asn Asp Thr Met Asp Lys Leu Ser Ala Ile 1985 1990 1995 2000
- Thr Asn Asp Thr Ala Ala Lys Leu Gln Ala Val Lys Glu Lys Ala Arg 2005 2010 2015
- Glu Ala Asn Asp Thr Ala Lys Ala Val Leu Ala Gln Val Lys Asp Leu 2020 2025 2030
- His Gln Asn Leu Asp Gly Leu Lys Gln Asn Tyr Asn Lys Leu Ala Asp 2035 2040 2045
- Ser Val Ala Lys Thr Asn Ala Val Val Lys Asp Pro Ser Lys Asn Lys 2050 2055 2060
- Ile Ile Ala Asp Ala Gly Thr Ser Val Arg Asn Leu Glu Gln Glu Ala 2065 2070 2075 2080
- Asp Arg Leu Ile Asp Lys Leu Lys Pro Ile Lys Glu Leu Glu Asp Asn 2085 2090 2095
- Leu Lys Lys Asn Ile Ser Glu Ile Lys Glu Leu Ile Asn Gln Ala Arg 2100 2105 2110
- Lys Gln Ala Asn Ser Ile Lys Val Ser Val Ser Ser Gly Gly Asp Cys 2115 2120 2125
- Val Arg Thr Tyr Arg Pro Glu Ile Lys Lys Gly Ser Tyr Asn Asn Ile 2130 2135 2140
- Val Val His Val Lys Thr Ala Val Ala Asp Asn Leu Leu Phe Tyr Leu 2145 2150 2155 2160
- Gly Ser Ala Lys Phe Ile Asp Phe Leu Ala Ile Glu Met Arg Lys Gly 2165 2170 2175
- Lys Val Ser Phe Leu Trp Ile Val Gly Ser Gly Val Gly Arg Val Gly 2180 2185 2190
- Phe Pro Asp Leu Thr Ile Asp Asp Ser Tyr Trp Tyr Arg Ile Glu Ala 2195 2200 2205
- Ser Arg Thr Gly Arg Asn Gly Ser Ile Ser Val Arg Ala Leu Asp Gly 2210 2215 2220
- Pro Lys Ala Ser Met Val Pro Ser Thr Tyr His Ser Val Ser Pro Pro 2225 2230 2235 2240
- Gly Tyr Thr Ile Leu Asp Val Asp Ala Asn Ala Met Leu Phe Val Gly 2245 2250 2255
- Gly Leu Thr Gly Lys Ile Lys Lys Ala Asp Ala Val Arg Val Ile Thr 2260 2265 2270

Phe Thr Gly Cys Met Gly Glu Thr Tyr Phe Asp Asn Lys Pro Ile Gly 2275 2280 2285

- Leu Trp Asn Phe Arg Glu Lys Glu Gly Asp Cys Lys Gly Cys Thr Val 2290 2295 2300
- Ser Pro Gln Val Glu Asp Ser Glu Gly Thr Ile Gln Phe Asp Gly Glu 2305 2310 2315 2320
- Gly Tyr Ala Leu Val Ser Arg Pro Ile Arg Trp Tyr Pro Asn Ile Ser 2325 2330 2335
- Thr Val Met Phe Lys Phe Arg Thr Phe Ser Ser Ser Ala Leu Leu Met 2340 2345 2350
- Tyr Leu Ala Thr Arg Asp Leu Lys Asp Phe Met Ser Val Glu Leu Ser 2355 2360 2365
- Asp Gly His Val Lys Val Ser Tyr Asp Leu Gly Ser Gly Met Thr Ser 2370 2375 2380
- Val Val Ser Asn Gln Asn His Asn Asp Gly Lys Trp Lys Ala Phe Thr 2385 2390 2395 2400
- Leu Ser Arg Ile Gln Lys Gln Ala Asn Ile Ser Ile Val Asp Ile Asp 2405 2410 2415
- Ser Asn Gln Glu Glu Asn Val Ala Thr Ser Ser Ser Gly Asn Asn Phe  $2420 \hspace{1.5cm} 2425 \hspace{1.5cm} 2430$
- Gly Leu Asp Leu Lys Ala Asp Asp Lys Ile Tyr Phe Gly Gly Leu Pro 2435 2440 2445
- Thr Leu Arg Asn Leu Ser Met Lys Ala Arg Pro Glu Val Asn Val Lys 2450 2455 2460
- Lys Tyr Ser Gly Cys Leu Lys Asp Ile Glu Ile Ser Arg Thr Pro Tyr 2465 2470 2475 2480
- Asn Ile Leu Ser Ser Pro Asp Tyr Val Gly Val Thr Lys Gly Cys Ser 2485 2490 2495
- Leu Glu Asn Val Asn Thr Val Ser Phe Pro Lys Pro Gly Phe Val Glu 2500 2505 2510
- Leu Ala Ala Val Ser Ile Asp Val Gly Thr Glu Ile Asn Leu Ser Phe 2515 2520 2525
- Ser Thr Arg Asn Glu Ser Gly Ile Ile Leu Leu Gly Ser Gly Gly Thr  $2530 \\ \hspace{1.5cm} 2535 \\ \hspace{1.5cm} 2540$
- Leu Thr Pro Pro Arg Arg Lys Arg Arg Gln Thr Thr Gln Ala Tyr Tyr 2545 2550 2555 2560
- Ala Ile Phe Leu Asn Lys Gly Arg Leu Glu Val His Leu Ser Ser Gly 2565 2570 2575
- Thr Arg Thr Met Arg Lys Ile Val Ile Lys Pro Glu Pro Asn Leu Phe 2580 2585 2590
- His Asp Gly Arg Glu His Ser Val His Val Glu Arg Thr Arg Gly Ile

2595 2600 2605

- Phe Thr Val Gln Ile Asp Glu Asp Arg Arg His Ile Gln Asn Leu Thr 2610 2615 2620
- Glu Glu Gln Pro Ile Glu Val Lys Lys Leu Phe Val Gly Gly Ala Pro 2625 2630 2635 2640
- Pro Glu Phe Gln Pro Ser Pro Leu Arg Asn Ile Pro Ala Phe Gln Gly 2645 2650 2655
- Cys Val Trp Asn Leu Val Ile Asn Ser Ile Pro Met Asp Phe Ala Gln 2660 2665 2670
- Pro Ile Ala Phe Lys Asn Ala Asp Ile Gly Arg Cys Thr Tyr Gln Lys 2675 2680 2685
- Pro Arg Glu Asp Glu Ser Glu Ala Val Pro Ala Glu Val Ile Val Gln 2690 2695 2700
- Pro Gln Ser Val Pro Thr Pro Ala Phe Pro Phe Pro Val Pro Thr Met 2705 2710 2715 2720
- Val His Gly Pro Cys Val Ala Glu Ser Glu Pro Ala Leu Leu Thr Gly 2725 2730 2735
- Ser Lys Gln Phe Gly Leu Ser Arg Asn Ser His Ile Ala Ile Val Phe 2740 2745 2750
- Asp Asp Thr Lys Val Lys Asn Arg Leu Thr Ile Glu Leu Glu Val Arg 2755 2760 2765
- Thr Glu Ala Glu Ser Gly Leu Leu Phe Tyr Met Gly Arg Ile Asn His 2770 2775 2780
- Ala Asp Phe Gly Thr Val Gln Leu Arg Asn Gly Phe Pro Phe Phe Ser 2785 2790 2795 2800
- Tyr Asp Leu Gly Ser Gly Ser Thr Arg Thr Met Ile Pro Thr Lys Ile 2805 2810 2815
- Asn Asp Gly Gln Trp His Lys Ile Lys Ile Val Arg Val Lys Gln Glu 2820 2825 2830
- Gly Ile Leu Tyr Val Asp Asp Ala Ser Ser Gln Thr Ile Ser Pro Lys 2835 2840 2845
- Lys Ala Asp Ile Leu Asp Val Gly Gly Ile Leu Tyr Val Gly Gly Leu 2850 2855 2860
- Pro Ile Asn Tyr Thr Thr Arg Arg Ile Gly Pro Val Thr Tyr Ser Leu 2865 2870 2875 2880
- Asp Gly Cys Val Arg Asn Leu His Met Glu Gln Ala Pro Val Asp Leu 2885 2890 2895
- Asp Gln Pro Thr Ser Ser Phe His Val Gly Thr Cys Phe Ala Asn Ala 2900 2905 2910
- Glu Ser Gly Thr Tyr Phe Asp Gly Thr Gly Phe Gly Lys Ala Val Gly 2915 2920 2925

Gly Phe Ile Val Gly Leu Asp Leu Leu Val Glu Phe Glu Phe Arg Thr 2935 Thr Arg Pro Thr Gly Val Leu Leu Gly Ile Ser Ser Gln Lys Met Asp Gly Met Gly Ile Glu Met Ile Asp Glu Lys Leu Met Phe His Val Asp 2970 Asn Gly Ala Gly Arg Phe Thr Ala Ile Tyr Asp Ala Glu Ile Pro Gly 2985 His Met Cys Asn Gly Gln Trp Tyr Lys Val Thr Ala Lys Lys Ile Lys Asn Arg Leu Glu Leu Val Val Asp Gly Asn Gln Val Asp Ala Gln Ser 3015 Pro Asn Ser Ala Ser Thr Ser Ala Asp Thr Asn Asp Pro Val Phe Val 3030 3035 Gly Gly Phe Pro Gly Gly Leu Asn Gln Phe Gly Leu Thr Thr Asn Ile 3045 3050 Arg Phe Arg Gly Cys Ile Arg Ser Leu Lys Leu Thr Lys Gly Thr Ala Asn Arg Trp Arg Leu Ile Leu Pro Arg Pro Trp Asn 3075 <210> 13 <211> 5613 <212> DNA <213> Homo sapiens <221> CDS <222> (118) .. (5475) <220> <221> sig\_peptide <222> (118) . . (180) <400> 13 cccggagcag ggcgagagct cgcgtcgccg gaaaggaaga cgggaagaaa gggcaggcgg 60 ctcggcgggc gtcttctcca ctcctctgcc gcgtccccgt ggctgcaggg agecggc atg ggg ctt ctc cag ttg cta gct ttc agt ttc tta gcc ctg tgc aga 165 Met Gly Leu Leu Gln Leu Leu Ala Phe Ser Phe Leu Ala Leu Cys Arg

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tgt Cys 65	atc Ile	gtc Val	agc Ser	cac His	ttg Leu 70	cag Gln	gag Glu	gac Asp	aaa Lys	aaa Lys 75	tgc Cys	ttc Phe	ata Ile	tgc Cys	aat Asn 80	357
			cct Pro													405
			gtc Val 100													453
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			cat His													549
			atg Met													597
			aga Arg													645
			ggc Gly 180													693
			gac Asp													741
			cct Pro													789
			tta Leu													837
			gga Gly													885
			tat Tyr 260													933
			cat His													981

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Thr Met	: Gly														1269
cca gag Pro Gli 385															1317
gac cca Asp Pro															1365
ttt tc															1413
gaa gga Glu Gly															1461
agt gad Ser Glu 450	ı Āsp														1509
aca ato Thr Ile 465															1557
tgc aag Cys Lys															1605
cac tgg															1653
gac ct: Asp Le															1701
tgc tca	a tgc	cgg	cct	cac	atg	att	gga	cgt	cag	tgc	aac	gaa	gtg	gaa	1749

Сув	Ser 530	Сув	Arg	Pro	His	Met 535	Ile	Gly	Arg	Gln	Сув 540	Asn	Glu	Val	Glu	
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gaa Glu	gcc Ala	aac Asn	ttg Leu	999 Gly 565	cct Pro	ggg Gly	gtt Val	agc Ser	ata Ile 570	gtg Val	gag Glu	cgg Arg	caa Gln	tat Tyr 575	atc Ile	1845
			att Ile 580													1893
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			atc Ile													1989
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			ggt Gly													2085
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			aca Thr													2181
			agc Ser													2229
gtt Val 705	ctc Leu	atg Met	cca Pro	tac Tyr	tgt Cys 710	aaa Lys	tca Ser	ctg Leu	gac Asp	atc Ile 715	ttc Phe	acc Thr	gtg Val	gga Gly	ggt Gly 720	2277
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			aga Arg													2421
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tgc aat ccc gtc act ggc cag tgc cac tgt ttc cag gga gtg tat gct 2661 Cys Asn Pro Val Thr Gly Gln Cys His Cys Phe Gln Gly Val Tyr Ala

cgg cag tgt gat cgg tgc tta cct ggg cac tgg ggc ttt cca agt tgc 2709 Arg Gln Cys Asp Arg Cys Leu Pro Gly His Trp Gly Phe Pro Ser Cys

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Gln Pro Cys Gln Cys Asn Gly His Ala Asp Asp Cys Asp Pro Val Thr
865 870 875 880

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gtt tgt gat cct gga tac att ggt tcc aga tgt gac gac tgt gcc tca 2997
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	Val					Gly					Lys			cga Arg		3621
Tyr					Pro					Cys				ttt Phe		3669
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		Thr					Glu					Glu		aaa Lys		3813
	Leu					Ala					Lys			G1y 999		3861
Leu					Glu					Asp				atg Met		3909

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gat Asp	Ile	cgg Arg 1315	ggt Gly	gcc Ala	ttg Leu	Asp	agc Ser 1320	att Ile	acc Thr	aag Lys	${\tt Tyr}$	ttc Phe 1325	cag Gln	atg Met	tct Ser	4101
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	Ala					Gly		ccc Pro			Āla					4341
Ala act Thr	Ala gaa	Glu 1395 tgt	Met ggc	Thr 999	Cys cca Pro	Gly aac	Thr 1400 tgc		Pro act	Gly gac Asp	Ala gaa	Ser 1405 gga	Cys	Ser agg	Glu	4341 4389
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caa Gln	agt Ser	gca Ala	gaa Glu 1	gat Asp 685	gtt Val	aag Lys	aag Lys	Thr	tta Leu .690	gat Asp	ggt Gly	gaa Glu	Leu	gat Asp .695	gaa Glu	5205
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	Asp		aga Arg			Ala					Asn					5301
Leu			caa Gln		Asn					Leu						5349
aga Arg	aaa Lys	tat Tyr	gaa Glu	gac Asp	aat Asn	caa Gln	aga Arg	tac Tyr	tta Leu	gaa Glu	gat Asp	aaa Lys	gct Ala	caa Gln	gaa Glu	5397

1755

1760

1750

1745

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Ala Leu Asp Pro Ala Phe Lys Ile Glu Asp Pro Tyr Ser Pro Arg Ile

215 220 Gln Asn Leu Leu Lys Ile Thr Asn Leu Arg Ile Lys Phe Val Lys Leu 235 His Thr Leu Gly Asp Asn Leu Leu Asp Ser Arg Met Glu Ile Arg Glu Lys Tyr Tyr Tyr Ala Val Tyr Asp Met Val Val Arg Gly Asn Cys Phe Cys Tyr Gly His Ala Ser Glu Cys Ala Pro Val Asp Gly Phe Asn Glu 275 280 285Glu Val Glu Gly Met Val His Gly His Cys Met Cys Arg His Asn Thr 290 295 300 Lys Gly Leu Asn Cys Glu Leu Cys Met Asp Phe Tyr His Asp Leu Pro 305 310 315 320Trp Arg Pro Ala Glu Gly Arg Asn Ser Asn Ala Cys Lys Lys Cys Asn 325  $\phantom{0}$  330  $\phantom{0}$  335 Cys Asn Glu His Ser Ile Ser Cys His Phe Asp Met Ala Val Tyr Leu  $340 \hspace{1.5cm} 345 \hspace{1.5cm} 350$ Ala Thr Gly Asn Val Ser Gly Gly Val Cys Asp Asp Cys Gln His Asn Thr Met Gly Arg Asn Cys Glu Gln Cys Lys Pro Phe Tyr Tyr Gln His Pro Glu Arg Asp Ile Arg Asp Pro Asn Phe Cys Glu Arg Cys Thr Cys Asp Pro Ala Gly Ser Gln Asn Glu Gly Ile Cys Asp Ser Tyr Thr Asp 405 410 415Phe Ser Thr Gly Leu Ile Ala Gly Gln Cys Arg Cys Lys Leu Asn Val Glu Gly Glu His Cys Asp Val Cys Lys Glu Gly Phe Tyr Asp Leu Ser Ser Glu Asp Pro Phe Gly Cys Lys Ser Cys Ala Cys Asn Pro Leu Gly 450 450 Thr Ile Pro Gly Gly Asn Pro Cys Asp Ser Glu Thr Gly His Cys Tyr 465 470 475 480 Cys Lys Arg Leu Val Thr Gly Gln His Cys Asp Gln Cys Leu Pro Glu 485 490 495His Trp Gly Leu Ser Asn Asp Leu Asp Gly Cys Arg Pro Cys Asp Cys 500 510 Asp Leu Gly Gly Ala Leu Asn Asn Ser Cys Phe Ala Glu Ser Gly Gln 515 520 525

Cys Ser Cys Arg Pro His Met Ile Gly Arg Gln Cys Asn Glu Val Glu 530 540

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Gln Pro Cys Gln Cys Asn Gly His Ala Asp Asp Cys Asp Pro Val Thr 865 870 875 880

- Gly Glu Cys Leu Asn Cys Gln Asp Tyr Thr Met Gly His Asn Cys Glu 885 890 895
- Arg Cys Leu Ala Gly Tyr Tyr Gly Asp Pro Ile Ile Gly Ser Gly Asp 900 905 910
- His Cys Arg Pro Cys Pro Cys Pro Asp Gly Pro Asp Ser Gly Arg Gln 915 920 925
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- Gln Ser Ala Glu Asp Val Lys Lys Thr Leu Asp Gly Glu Leu Asp Glu 1685 1690 1695
- Lys Tyr Lys Lys Val Glu Asn Leu Ile Ala Lys Lys Thr Glu Glu Ser 1700 1705 1710
- Ala Asp Ala Arg Arg Lys Ala Glu Met Leu Gln Asn Glu Ala Lys Thr 1715 1720 1725
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					cac His											144
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cat His 65	gag Glu	acc Thr	ctg Leu	aat Asn	ect Pro 70	gac Asp	agc Ser	cat His	ctc Leu	att Ile 75	gaa Glu	aat Asn	gtg Val	gtc Val	act Thr 80	240
aca Thr	ttt Phe	gct Ala	cca Pro	aac Asn 85	ege Arg	ctt Leu	aag Lys	att Ile	tgg Trp 90	tgg Trp	caa Gln	tct Ser	gaa Glu	aat Asn 95	ggt Gly	288
gtg Val	gaa Glu	aat Asn	gta Val 100	act Thr	atc Ile	caa Gln	ctg Leu	gat Asp 105	ttg Leu	gaa Glu	gca Ala	gaa Glu	ttc Phe 110	cat His	ttt Phe	336
					act Thr											384
					gac Asp											432
ttc Phe 145	gcc Ala	tat Tyr	gac Asp	tgt Cys	gag Glu 150	gcc Ala	tcg Ser	ttt Phe	cca Pro	99c Gly 155	att Ile	tca Ser	act Thr	ggc Gly	ccc Pro 160	480
					gac Asp											528
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					agg Arg 230											720

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gaa ct Glu Le 29	и Сув														912
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aca gg Thr Gl 465															1440

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gaa tgc gac Glu Cys Asp 755	Pro Gln					Pro As:		2304
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tgc tta cct Cys Leu Pro 835						Cys Gl		2544
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tgc cag gac Cys Gln Asp 865 tac tat ggc Tyr Tyr Gly	tac acc Tyr Thr  gac ccc Asp Pro 885 gat ggt Asp Gly 900 cct gtt	Asp Cys 855 atg ggt Met Gly 870 atc att Ile Ile ccc gac Pro Asp act tta	cat aac His Asi ggg tca Gly Sei agt gga Ser Gly 905	tgt gaa Cys Gli 87: a ggt gat Gly Asp 890 a cgc cag Arg Glr	a agg tgc a agg tgc a Arg Cys c cac tgc b His Cys g ttt gcc a Phe Ala	ttg gcc Leu Ald cgc ccc Arg Pro 899 agg agg Arg Ser 910 gat ccc Asp Pro	t ggt a ggy asso	26 <b>4</b> 0 2688
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tcg gtg gag agg aaa gtc Ser Val Glu Arg Lys Val 1205	. Ser Glu Ile I	ys Asp Ile Leu Ala	

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gat tot ota cag ac Asp Ser Leu Gln Th 1265				40
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cca aac tgc aga ac Pro Asn Cys Arg Th 1395		lu Arg Lys Cys (		24
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gaa aat tta att Glu Asn Leu Ile				
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Leu Gln Glu Asp Lys Lys Cys Phe Ile Cys Asn Ser Gln Asp Pro Tyr 50 55 60	
His Glu Thr Leu Asn Pro Asp Ser His Leu Ile Glu Asn Val Val Thr 65 70 75 80	
Thr Phe Ala Pro Asn Arg Leu Lys Ile Trp Trp Gln Ser Glu Asn Gly 85 90 95	
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Thr His Leu Ile Met Thr Phe Lys Thr Phe Arg Pro Ala Ala Met Leu 115 120 125	
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Met Lys Lys Val Asp Asp Ile Ile Cys Asp Ser Arg Tyr Ser Asp Ile	

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Phe	Lys	Ile 195	Glu	Asp	Pro	Tyr	Ser 200	Pro	Arg	Ile	Gln	Asn 205	Leu	Leu	Lys
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Asn	Pro 450	Сув	qaA	Ser	Glu	Thr 455	Gly	His	Cys	Tyr	Cys 460	Lys	Arg	Leu	Val

Thr Gly Gln His Cys Asp Gln Cys Leu Pro Glu His Trp Gly Leu Ser 465 470 475 480

Asn Asp Leu Asp Gly Cys Arg Pro Cys Asp Cys Asp Leu Gly Gly Ala 485  $\phantom{\bigg|}490\phantom{\bigg|}$ 

Leu Asn Asn Ser Cys Phe Ala Glu Ser Gly Gln Cys Ser Cys Arg Pro
500 505 510

- His Met Ile Gly Arg Gln Cys Asn Glu Val Glu Pro Gly Tyr Tyr Phe 515 520 525
- Ala Thr Leu Asp His Tyr Leu Tyr Glu Ala Glu Glu Ala Asn Leu Gly 530 535 540
- Pro Gly Val Ser Ile Val Glu Arg Gln Tyr Ile Gln Asp Arg Ile Pro 545 550 555 560
- Ser Trp Thr Gly Ala Gly Phe Val Arg Val Pro Glu Gly Ala Tyr Leu 565 570 575
- Glu Phe Phe Ile Asp Asn Ile Pro Tyr Ser Met Glu Tyr Asp Ile Leu 580 585 590
- Ile Arg Tyr Glu Pro Gln Leu Pro Asp His Trp Glu Lys Ala Val Ile 595  $\,\,$  600  $\,\,$  605
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- Cys Lys Ser Leu Asp Ile Phe Thr Val Gly Gly Ser Gly Asp Gly Val
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- As Ser Arg Ser Val Val Lys Thr Pro Met Thr Asp Val Cys Arg As 725 730 735
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- Glu Cys Asp Pro Gln Gly Ser Leu Ser Ser Val Cys Asp Pro Asn Gly 755 760 765
- Gly Gln Cys Gln Cys Arg Pro Asn Val Val Gly Arg Thr Cys Asn Arg 770 785 780
- Cys Ala Pro Gly Thr Phe Gly Phe Gly Pro Ser Gly Cys Lys Pro Cys 785 790 795 800
- Glu Cys His Leu Gln Gly Ser Val Asn Ala Phe Cys Asn Pro Val Thr 805 810 815

Gly Gln Cys His Cys Phe Gln Gly Val Tyr Ala Arg Gln Cys Asp Arg 820 825 830

- Cys Leu Pro Gly His Trp Gly Phe Pro Ser Cys Gln Pro Cys Gln Cys 835 840 845
- Asn Gly His Ala Asp Asp Cys Asp Pro Val Thr Gly Glu Cys Leu Asn 850 855 860
- Cys Gln Asp Tyr Thr Met Gly His Asn Cys Glu Arg Cys Leu Ala Gly 865 870 875 880
- Tyr Tyr Gly Asp Pro Ile Ile Gly Ser Gly Asp His Cys Arg Pro Cys 885 890 895
- Pro Cys Pro Asp Gly Pro Asp Ser Gly Arg Gln Phe Ala Arg Ser Cys 900 905 910
- Tyr Gln Asp Pro Val Thr Leu Gln Leu Ala Cys Val Cys Asp Pro Gly 915 920 925
- Tyr Ile Gly Ser Arg Cys Asp Asp Cys Ala Ser Gly Tyr Phe Gly Asn 930 935 940
- Pro Ser Glu Val Gly Gly Ser Cys Gln Pro Cys Gln Cys His Asn Asn 945 950 955 960
- Ile Asp Thr Thr Asp Pro Glu Ala Cys Asp Lys Glu Thr Gly Arg Cys 965 970 975
- Leu Lys Cys Leu Tyr His Thr Glu Gly Glu His Cys Gln Phe Cys Arg 980 985 990
- Phe Gly Tyr Tyr Gly Asp Ala Leu Arg Gln Asp Cys Arg Lys Cys Val 995 1000 1005
- Cys Asn Tyr Leu Gly Thr Val Gln Glu His Cys Asn Gly Ser Asp Cys 1010 1015 1020
- Gln Cys Asp Lys Ala Thr Gly Gln Cys Leu Cys Leu Pro Asn Val Ile 1025 1030 1035 1040
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1140 1145 1150

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- Leu Asp Ser Ile Thr Lys Tyr Phe Gln Met Ser Leu Glu Ala Glu Glu 1300 1305 1310
- Arg Val Asn Ala Ser Thr Thr Glu Pro Asn Ser Thr Val Glu Gln Ser 1315 1320 1325
- Ala Leu Met Arg Asp Arg Val Glu Asp Val Met Met Glu Arg Glu Ser 1330 1335 1340
- Gln Phe Lys Glu Lys Gln Glu Glu Gln Ala Arg Leu Leu Asp Glu Leu 1345 1350 1355 1360
- Ala Gly Lys Leu Gln Ser Leu Asp Leu Ser Ala Ala Ala Glu Met Thr 1365 1370 1375
- Cys Gly Thr Pro Pro Gly Ala Ser Cys Ser Glu Thr Glu Cys Gly Gly 1380 1385 1390
- Pro Asn Cys Arg Thr Asp Glu Gly Glu Arg Lys Cys Gly Gly Pro Gly
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- Ser Glu Cys Gly Gly Pro Asn Cys Arg Thr Asp Glu Gly Glu Lys Lys 1410 1415 1420
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- Asn Ser Gly Glu Ala Glu Tyr Ile Glu Lys Val Val Tyr Ser Val Lys 1665 1670 1675 1680

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Ile Cys Asp Ser Arg Asp Pro Tyr His Glu Thr Leu Asn Pro Asp Ser

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		aac Asn 755														2304
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	qaA		agg Arg			Glu					Asp					3264

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Lys Thr Trp Gly Val Tyr Arg Tyr Phe Ala Tyr Asp Cys Glu Ser Ser 100 105 110

Phe Pro Gly Ile Ser Thr Gly Pro Met Lys Lys Val Asp Asp Ile Ile 115 120 125

Cys Asp Ser Arg Tyr Ser Asp Ile Glu Pro Ser Thr Glu Gly Glu Val

Pro Arg Ile Gln Asn Leu Leu Lys Ile Thr Asn Leu Arg Ile Lys Phe 165 170 175

Val Lys Leu His Thr Leu Gly Asp Asn Leu Leu Asp Ser Arg Met Glu 180 185 190

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Asn Cys Phe Cys Tyr Gly His Ala Ser Glu Cys Ala Pro Val Asp Gly 210 215 220

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His Asn Thr Lys Gly Leu Asn Cys Glu Leu Cys Met Asp Phe Tyr His 245 250 255

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Lys Cys Asn Cys Asn Glu His Ser Ser Ser Cys His Phe Asp Met Ala 275 280 285

Val Phe Leu Ala Thr Gly Asn Val Ser Gly Gly Val Cys Asp Asn Cys 290 295 300

Gln His Asn Thr Met Gly Arg Asn Cys Glu Gln Cys Lys Pro Phe Tyr 305 310 315 320

Phe Gln His Pro Glu Arg Asp Ile Arg Asp Pro Asn Leu Cys Glu Pro 325 330 335

Cys Thr Cys Asp Pro Ala Gly Ser Glu Asn Gly Gly Ile Cys Asp Gly 340 345 350

Tyr Thr Asp Phe Ser Val Gly Leu Ile Ala Gly Gln Cys Arg Cys Lys 355 360 365

Leu His Val Glu Gly Glu Arg Cys Asp Val Cys Lys Glu Gly Phe Tyr 370 380

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500 505 510 Gln Tyr Ile Gln Asp Arg Ile Pro Ser Trp Thr Gly Pro Gly Phe Val 515 520 525 Arg Val Pro Glu Gly Ala Tyr Leu Glu Phe Phe Ile Asp Asn Ile Pro 530 535 540 Tyr Ser Met Glu Tyr Glu Ile Leu Ile Arg Tyr Glu Pro Gln Leu Pro 545 550 555 560 Asp His Trp Glu Lys Ala Val Ile Thr Val Gln Arg Pro Gly Lys Ile 565 570 575 Pro Ala Ser Ser Arg Cys Gly Asn Thr Val Pro Asp Asp Asp Asn Gln 585 Val Val Ser Leu Ser Pro Gly Ser Arg Tyr Val Val Leu Pro Arg Pro 600 Val Cys Phe Glu Lys Gly Met Asn Tyr Thr Val Arg Leu Glu Leu Pro 610 615 620 Gln Tyr Thr Ala Ser Gly Ser Asp Val Glu Ser Pro Tyr Thr Phe Ile Asp Ser Leu Val Leu Met Pro Tyr Cys Lys Ser Leu Asp Ile Phe Thr Val Gly Gly Ser Gly Asp Gly Glu Val Thr Asn Ser Ala Trp Glu Thr Phe Gln Arg Tyr Arg Cys Leu Glu Asn Ser Arg Ser Val Val Lys Thr

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1035

1030

1025

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1290

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- Ser Val Lys Gln Asn Ala Asp Asp Val Lys Lys Thr Leu Asp Gly Glu 1620 1625 1630
- Leu Asp Glu Lys Tyr Lys Lys Val Glu Ser Leu Ile Ala Gln Lys Thr 1635 1640 1645
- Glu Glu Ser Ala Asp Ala Arg Arg Lys Ala Glu Leu Leu Gln Asn Glu 1650 1655 1660
- Ala Lys Thr Leu Leu Ala Gln Ala Asn Ser Lys Leu Gln Leu Leu Glu 1665 1670 1675 1680

Asp Leu Glu Arg Lys Tyr Glu Asp Asn Gln Lys Tyr Leu Glu Asp Lys 1690

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Met Arg Gly Ser His Arg Ala Ala Pro Ala Leu

340

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ggc ggg cgg ccg cag cgc tgc atg ccc gag ttc gtc aac gcc gct ttc 436 Gly Gly Arg Pro Gln Arg Cys Met Pro Glu Phe Val Asn Ala Ala Phe 50

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cgc ccg gag a Arg Pro Glu S					Pro
tgg att cct t Trp Ile Pro T			y Ser Cys Glu		
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gtg gcc ttt to Val Ala Phe S 220					
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act ctt aat c Thr Leu Asn A 2			y Asp Glu Val		
aaa gtt ctc a Lys Val Leu L 270					
and and tot a					
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Gly Arg Cys L	ys Cys Asn	Gly His Al 290 aat tgc aa	a Ser Glu Cys 295 a cat aac aca	Met Lys Asn	Glu gac 1204
Gly Arg Cys L 285 ttt gat aag c Phe Asp Lys L	tg gtg tgt eu Val Cys 305 gt ctt cct	Gly His Al- 290 aat tgc aa. Asn Cys Ly	a Ser Glu Cys 295 a cat aac aca s His Asn Thr 310 t gac cgg ccg	tat gga gta Tyr Gly Val	gac 1204 Asp 315 gca 1252 Ala
Cys Glu Lys Cys Glu School Cys Glu Lys Cys Glu School Cys Glu Scho	ys Cys Asn  tg gtg tgt eu Val Cys 305 gt ctt cct ys Leu Pro 320 gt gcc agt	Gly His Al. 290  aat tgc aa Asn Cys Ly  ttc ttc aa Phe Phe As: gaa tgc ct	a Ser Glu Cys 295  a cat aac aca 8 His Asn Thr 310  t gac cgg ccg n Asp Arg Pro 325  g ccc tgt gat u Pro Cys Asp	Met Lys Asn tat gga gta Tyr Gly Val tgg agg agg Trp Arg Arg 330 tgc aat ggt	gac 1204 Asp 315 gca 1252 Ala

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	tat Tyr							2164
	ctt Leu							2212
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Lys Thr Arg Glu 1405	Ala Gln Gln A 1410	Ala Leu Gly Ser	get geg geg gat gee Ala Ala Ala Asp Ala 1415	
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Gln Asp Met Met 1485	Met Ala Gly M 1490	Met Ala Ser Gln	gct gct caa gaa gcc Ala Ala Gln Glu Ala 1495	4756
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Arg Cys Met Pro Glu Phe Val Asn Ala Ala Phe Asn Val Thr Val Val 50 55 60

Ala Thr Asn Thr Cys Gly Thr Pro Pro Glu Glu Tyr Cys Val Gln Thr 65 70 75 80

Gly Val Thr Gly Val Thr Lys Ser Cys His Leu Cys Asp Ala Gly Gln
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Pro His Leu Gln His Gly Ala Ala Phe Leu Thr Asp Tyr Asn Asn Gln 100 105 110

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115 120 125

Tyr Pro Ser Ser Ile Asn Leu Thr Leu His Leu Gly Lys Ala Phe Asp 130 135 140

Ile Thr Tyr Val Arg Leu Lys Phe His Thr Ser Arg Pro Glu Ser Phe 145 150 155 160

Ala Ile Tyr Lys Arg Thr Arg Glu Asp Gly Pro Trp Ile Pro Tyr Gln 165 170 175

Tyr Tyr Ser Gly Ser Cys Glu Asn Thr Tyr Ser Lys Ala Asn Arg Gly 180 185 190

Phe Ile Arg Thr Gly Gly Asp Glu Gln Gln Ala Leu Cys Thr Asp Glu

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Leu 225	Glu	Gly	Arg	Pro	Ser 230	Ala	Tyr	Asn	Phe	Авр 235	Asn	Ser	Pro	Val	Leu 240
Gln	Glu	Trp	Val	Thr 245	Ala	Thr	Asp	Ile	Arg 250	Val	Thr	Leu	Asn	Arg 255	Leu
Asn	Thr	Phe	Gly 260	Asp	Glu	Val	Phe	Asn 265	Asp	Pro	Lys	Val	<b>Leu</b> 270	Lys	Ser
Tyr	Tyr	Tyr 275	Ala	Ile	Ser	Asp	Phe 280	Ala	Val	Gly	Gly	Arg 285	Сув	Lys	Сув
Asn	Gly 290	His	Ala	Ser	Glu	Cys 295	Met	Lув	Asn	Glu	Phe 300	Asp	ГÀв	Leu	Val
Cys 305	Asn	Cys	Lys	His	Asn 310	Thr	Tyr	Gly	Val	Asp 315	Сув	Glu	Lys	Cys	Leu 320
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Gly	Phe	His 435	Ser	Leu	Thr	Glu	Ala 440	Gly	Cys	Arg	Pro	Сув 445	Ser	Сув	Asp
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Cys Leu Lys Cys Ile Tyr Asn Thr Ala Gly Phe Tyr Cys Asp Arg Cys 850 850 860

- Lys Asp Gly Phe Phe Gly Asn Pro Leu Ala Pro Asn Pro Ala Asp Lys 865 870 880
- Cys Lys Ala Cys Asn Cys Asn Pro Tyr Gly Thr Met Lys Gln Gln Ser 885 890 895
- Ser Cys Asn Pro Val Thr Gly Gln Cys Glu Cys Leu Pro His Val Thr 900 905 910
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- Gly Gln Gly Cys Glu Arg Cys Asp Cys His Ala Leu Gly Ser Thr Asn 930 935 940
- Gly Gln Cys Asp Ile Arg Thr Gly Gln Cys Glu Cys Gln Pro Gly Ile 945 950 955 960
- Thr Gly Gln His Cys Glu Arg Cys Glu Val Asn His Phe Gly Phe Gly 965 970 975
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- Gly Asn Arg Cys Asp Gln Cys Glu Glu Asn Tyr Phe Tyr Asn Arg Ser 1010 1015 1020
- Trp Pro Gly Cys Gln Glu Cys Pro Ala Cys Tyr Arg Leu Val Lys Asp 025 1030 1035
- Lys Val Ala Asp His Arg Val Lys Leu Glu Glu Leu Glu Ser Leu Ile 1045 1050 1055
- Ala Asn Leu Gly Thr Gly Asp Glu Met Val Thr Asp Gln Ala Phe Glu 1060 1065 1070
- Asp Arg Leu Lys Glu Ala Glu Arg Glu Val Met Asp Leu Leu Arg Glu 1075 1080 1085
- Ala Gln Asp Val Lys Asp Val Asp Gln Asn Leu Met Asp Arg Leu Gln 1090 1095 1100
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- His Val Glu Asn Thr Glu Arg Leu Ile Glu Ile Ala Ser Arg Glu Leu 1140 1145 1150
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- Lys Ala His Glu Ala Glu Arg Ile Ala Ser Ala Val Gln Lys Asn Ala 425 1430 1435 1440
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His Leu Gln His Gly Ala Ala Phe Leu Thr Asp Tyr Asn Asn Gln Ala
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			gac Asp													912
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	Gly 999															1440
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	aga Arg															1536
	atc Ile		ata													
		Ala 515	val													1584
	gca Ala 530	515 aag	Val	Ile ttg	Ser ggc	Asp	Ser 520 cag	Tyr gtg	Phe ttg	Pro agt	Arg	Tyr 525 ggt	Phe cag	Ile aac	Ala	1584
Pro	gca Ala	aag Lys tcc	val ttc Phe ttt	Ile ttg Leu cga	Ser ggc Gly gtg	Asp aag Lys 535 gac	Ser 520 cag Gln	Tyr gtg Val cga	Phe ttg Leu gat	Pro agt Ser	tat Tyr 540	Tyr 525 ggt Gly ctc	Phe cag Gln tct	Ile aac Asn	Ala ctc Leu gaa	
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Pro tcc Ser 545 gac Asp	gca Ala 530 ttc Phe	aag Lys tcc Ser gtg Val	val ttc Phe ttt Phe ctt Leu	ttg Leu cga Arg gag Glu 565	ggc Gly gtg Val 550 gga Gly	aag Lys 535 gac Asp gct Ala	ser 520 cag Gln agg Arg ggc Gly	gtg Val cga Arg tta Leu	ttg Leu gat Asp aga Arg 570	agt Ser act Thr 555 gta Val	tat Tyr 540 cgc Arg tct Ser	Tyr 525 ggt Gly ctc Leu gta Val	Phe cag Gln tct Ser ccc Pro	aac Asn gcc Ala ttg Leu 575	Ala ctc Leu gaa Glu 560 atc Ile	1632

595	600		605	
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			t gat gtc acc ctg 1920 p Asp Val Thr Leu 640	•
			t tgg gtg gag tcc 1968 r Trp Val Glu Ser 655	:
			t gag atg tgc ctc 2016 s Glu Met Cys Leu 670	
		Asn Leu Gly Pro	a tac agt cca tgt 2064 o Tyr Ser Pro Cys 685	
			t gat cct gag aca 2112 3 Asp Pro Glu Thr 0	
			g cac tgt gag aag 2160 o His Cys Glu Lys 720	
			e acc tcc tcc gat 2208 y Thr Ser Ser Asp 735	
			get gtt gtt ccc 2256 s Ala Val Val Pro 750	
		Asn Cys Pro Th	ggc acc act ggt 2304 r Gly Thr Thr Gly 765	
			a gac ccc ctg ggt 2352 y Asp Pro Leu Gly )	
			g tgc agt gac aac 2400 n Cys Ser Asp Asn 800	
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			ggt Gly													2688
			gag Glu 900													2736
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			cag Gln			Pro					Leu					3024
Val			cat His		Val					Leu						3072
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		Val	aaa Lys 1060				Gln					Arg				3216
	Asn		act Thr			Ser					Leu					3264

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gta Val 1105	Glu	aac Asn	aca Thr	Glu	cgg Arg 1110	ttg Leu	att Ile	gaa Glu	Ile	gca Ala 1115	tcc Ser	aga Arg	gaa Glu	Leu	gag Glu 1120	3360
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	Ala	gaa Glu 1155				Gln					Ile					3504
Lys		gcc Ala			Thr					Tyr						3552
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		cga Arg					Ala					Asp				3696
	Ile	tat Tyr 1235				Ala					Leu					3744
Leu		aat Asn			Asn					Glu						3792
	Leu	att Ile		Gln					Tyr					Glu		3840
		gly 999	Lys					Lys					Lys			3888
		cag Gln					Gln					Ala				3936
	Ala	ctc Leu 1315				Ala					Arg					3984
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		Glu Ala Asn		ga gaa gcc cag 4 urg Glu Ala Gln 1375	128
Gln Ala Leu				cc aag aac aag 4 la Lys Asn Lys 1390	176
gcc cat gag Ala His Glu 1395	Ala Glu Arg	atc gca agc Ile Ala Ser 1400	Ala Val Gln L	ag aat gcc acc 4 ys Asn Ala Thr .05	224
	Ala Glu Ala			tt aca gat ctg 4 al Thr Asp Leu	272
				aa gca gaa aaa 4 lu Ala Glu Lys 1440	320
		Asp Asp Ala		tg atg atg gca 4 let Met Met Ala 1455	368
Gly Met Ala	tca cag gct Ser Gln Ala 1460	gct caa gaa Ala Gln Glu 1465	gcc gag atc a Ala Glu Ile A	at gcc aga aaa 4 sn Ala Arg Lys 1470	416
gcc aaa aac Ala Lys Asn 1475	Ser Val Thr	agc ctc ctc Ser Leu Leu 1480	Ser Ile Ile A	at gac ctc ttg 4 sn Asp Leu Leu 85	464
gag cag ctg Glu Gln Leu 1490	Gly Gln Leu	gat aca gtg Asp Thr Val .495	gac ctg aat a Asp Leu Asn L 1500	ag cta aac gag 4 ys Leu Asn Glu	512
				ag gtc agc gat 4 ys Val Ser Asp 1520	560
		Asp Leu Glu		ag aag cag gag 4 ys Lys Gln Glu 1535	608
Ala Ala Ile				tc atg aag gac 4 le Met Lys Asp 1550	656
	Leu Glu Asp		Thr Leu Pro S	ct ggc tgc ttc 4 er Gly Cys Phe 65	704
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His Leu Gln His Gly Ala Ala Phe Leu Thr Asp Tyr Asn Asn Gln Ala 65 70 75 80

Asp Thr Thr Trp Trp Gln Ser Gln Thr Met Leu Ala Gly Val Gln Tyr

Pro Ser Ser Ile Asn Leu Thr Leu His Leu Gly Lys Ala Phe Asp Ile

Thr Tyr Val Arg Leu Lys Phe His Thr Ser Arg Pro Glu Ser Phe Ala 115 120 125

Ile Tyr Lys Arg Thr Arg Glu Asp Gly Pro Trp Ile Pro Tyr Gln Tyr 130  $$135\$ 

Tyr Ser Gly Ser Cys Glu Asn Thr Tyr Ser Lys Ala Asn Arg Gly Phe 145 150 155 160

Ile Arg Thr Gly Gly Asp Glu Gln Gln Ala Leu Cys Thr Asp Glu Phe \$165\$

Ser Asp Ile Ser Pro Leu Thr Gly Gly Asn Val Ala Phe Ser Thr Leu

Glu Gly Arg Pro Ser Ala Tyr Asn Phe Asp Asn Ser Pro Val Leu Gln 195 200 205

Glu Trp Val Thr Ala Thr Asp Ile Arg Val Thr Leu Asn Arg Leu Asn 210  $\phantom{\bigg|}215\phantom{\bigg|}$  220

Thr Phe Gly Asp Glu Val Phe Asn Asp Pro Lys Val Leu Lys Ser Tyr 225 230 235

Tyr Tyr Ala Ile Ser Asp Phe Ala Val Gly Gly Arg Cys Lys Cys Asn 245 250 255 Gly His Ala Ser Glu Cys Met Lys Asn Glu Phe Asp Lys Leu Val Cys Asn Cys Lys His Asn Thr Tyr Gly Val Asp Cys Glu Lys Cys Leu Pro Phe Phe Asn Asp Arg Pro Trp Arg Arg Ala Thr Ala Glu Ser Ala Ser 290 295 300 Glu Cys Leu Pro Cys Asp Cys Asn Gly Arg Ser Gln Glu Cys Tyr Phe 305 310 315 320 Asp Pro Glu Leu Tyr Arg Ser Thr Gly His Gly Gly His Cys Thr Asn 325 330 335 Cys Gln Asp Asn Thr Asp Gly Ala His Cys Glu Arg Cys Arg Glu Asn 340 345 350Phe Phe Arg Leu Gly Asn Asn Glu Ala Cys Ser Ser Cys His Cys Ser 355 360 365 Pro Val Gly Ser Leu Ser Thr Gln Cys Asp Ser Tyr Gly Arg Cys Ser 370 380 Cys Lys Pro Gly Val Met Gly Asp Lys Cys Asp Arg Cys Gln Pro Gly 385 390 395 400 Phe His Ser Leu Thr Glu Ala Gly Cys Arg Pro Cys Ser Cys Asp Pro 405 410 415Ser Gly Ser Ile Asp Glu Cys Asn Val Glu Thr Gly Arg Cys Val Cys 420 425 430 Lys Asp Asn Val Glu Gly Phe Asn Cys Glu Arg Cys Lys Pro Gly Phe Phe Asn Leu Glu Ser Ser Asn Pro Arg Gly Cys Thr Pro Cys Phe Cys Phe Gly His Ser Ser Val Cys Thr Asn Ala Val Gly Tyr Ser Val Tyr 465 470 475 480 Ser Ile Ser Ser Thr Phe Gln Ile Asp Glu Asp Gly Trp Arg Ala Glu 485  $\phantom{\bigg|}485$ Gln Arg Asp Gly Ser Glu Ala Ser Leu Glu Trp Ser Ser Glu Arg Gln Asp Ile Ala Val Ile Ser Asp Ser Tyr Phe Pro Arg Tyr Phe Ile Ala 515 520 525 Pro Ala Lys Phe Leu Gly Lys Gln Val Leu Ser Tyr Gly Gln Asn Leu 530 535 Ser Phe Ser Phe Arg Val Asp Arg Arg Asp Thr Arg Leu Ser Ala Glu 545 550 555 560

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890 895 Gln Gly Cys Glu Arg Cys Asp Cys His Ala Leu Gly Ser Thr Asn Gly 905 Gln Cys Asp Ile Arg Thr Gly Gln Cys Glu Cys Gln Pro Gly Ile Thr 920 Gly Gln His Cys Glu Arg Cys Glu Val Asn His Phe Gly Phe Gly Pro Glu Gly Cys Lys Pro Cys Asp Cys His Pro Glu Gly Ser Leu Ser Leu Gln Cys Lys Asp Asp Gly Arg Cys Glu Cys Arg Glu Gly Phe Val Gly Asn Arg Cys Asp Gln Cys Glu Glu Asn Tyr Phe Tyr Asn Arg Ser Trp Pro Gly Cys Gln Glu Cys Pro Ala Cys Tyr Arg Leu Val Lys Asp Lys Val Ala Asp His Arg Val Lys Leu Gln Glu Leu Glu Ser Leu Ile Ala 1015 Asn Leu Gly Thr Gly Asp Glu Met Val Thr Asp Gln Ala Phe Glu Asp 1030 Arg Leu Lys Glu Ala Glu Arg Glu Val Met Asp Leu Leu Arg Glu Ala 1050 Gln Asp Val Lys Asp Val Asp Gln Asn Leu Met Asp Arg Leu Gln Arg 1065 Val Asn Asn Thr Leu Ser Ser Gln Ile Ser Arg Leu Gln Asn Ile Arg 1080 Asn Thr Ile Glu Glu Thr Gly Asn Leu Ala Glu Gln Ala Arg Ala His 1095 1100 Val Glu Asn Thr Glu Arg Leu Ile Glu Ile Ala Ser Arg Glu Leu Glu Lys Ala Lys Val Ala Ala Ala Asn Val Ser Val Thr Gln Pro Glu Ser 1130 Thr Gly Asp Pro Asn Asn Met Thr Leu Leu Ala Glu Glu Ala Arg Lys 1145 Leu Ala Glu Arg His Lys Gln Glu Ala Asp Asp Ile Val Arg Val Ala 1160 Lys Thr Ala Asn Asp Thr Ser Thr Glu Ala Tyr Asn Leu Leu Leu Arg

1195

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Arg Lys Tyr Glu Gln Ala Lys Asn Ile Ser Gln Asp Leu Glu Lys Gln

1190

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- Glu Ile Tyr Ala Ser Val Ala Gln Leu Ser Pro Leu Asp Ser Glu Thr 1235 1240 1245
- Leu Glu Asn Glu Ala Asn Asn Ile Lys Met Glu Ala Glu Asn Leu Glu 1250 1255 1260
- Gln Leu Ile Asp Gln Lys Leu Lys Asp Tyr Glu Asp Leu Arg Glu Asp 1265 1270 1275 1280
- Met Arg Gly Lys Glu Leu Glu Val Lys Asn Leu Leu Glu Lys Gly Lys 1285 1290 1295
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tgc gac gcc ggg cag ccc cac ctg cag cac ggg gca gcc ttc ctg acc

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	gcc Ala 125															676
	aaa Lys															724
	ccg Pro															772
	att Ile															820
	gca Ala															868
	tgt Cys 205															916 ,
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aac																
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580

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	gag Glu	Ser					Leu					Glu				3460
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cgt tta cag Arg Leu Gln	aat atc cgg Asn Ile Arg 1120	aat acc att Asn Thr Ile	gaa gag act Glu Glu Thr 1125	gga aac ttg gct Gly Asn Leu Ala 1130	3652
Glu Gln Ala	cgt gcc cat Arg Ala His 1135	gta gag aac Val Glu Asn 1140	Thr Glu Arg	ttg att gaa atc Leu Ile Glu Ile 1145	3700
gca tcc aga Ala Ser Arg 1150	gaa ctt gag Glu Leu Glu	aaa gca aaa Lys Ala Lys 1155	gtc gct gct Val Ala Ala	gcc aat gtg tca Ala Asn Val Ser 1160	3748
gtc act cag Val Thr Gln 1165	Pro Glu Ser	aca ggg gac Thr Gly Asp 1170	cca aac aac Pro Asn Asn 1175	atg act ctt ttg Met Thr Leu Leu	3796
				cag gaa gct gat Gln Glu Ala Asp 1195	3844
		Lys Thr Ala		tca act gag gca Ser Thr Glu Ala 1210	3892
Tyr Asn Leu	ctt ctg agg Leu Leu Arg 1215	aca ctg gca Thr Leu Ala 1220	Gly Glu Asn	caa aca gca ttt Gln Thr Ala Phe 1225	3940
				aag aac atc tca Lys Asn Ile Ser 1240	3988
	Glu Lys Gln			gag gcc aaa agg Glu Ala Lys Arg	4036
gcc ggt gac Ala Gly Asp 1260				gct cag ctg agc	4084
	Lys Ala Val 1265	Glu Ile Tyr	1270	1275	
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cct ttg gac Pro Leu Asp gaa gct gag Glu Ala Glu	tct gag aca Ser Glu Thr 1280 aat ctg gaa	ctg gag aat Leu Glu Asn	1270 gaa gca aat Glu Ala Asn 1285 gac cag aaa	1275 aac ata aag atg Asn Ile Lys Met	<b>4132</b> <b>4180</b>

1310	1315		1320	
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gcc cga gct gat gc Ala Arg Ala Asp Al 1340	t gcc aag gcc a Ala Lys Ala 1345	ctc gct gaa ga Leu Ala Glu Glu 1350	a gct gca aag aag u Ala Ala Lys Lys 1355	4324
gga cgg gat acc tt Gly Arg Asp Thr Le 136	u Gln Glu Ala	aat gac att cte Asn Asp Ile Lee 1365	c aac aac ctg aaa u Asn Asn Leu Lys 1370	4372
gat ttt gat agg cg Asp Phe Asp Arg Ar 1375	g Val Asn Asp	aac aag acg gco Asn Lys Thr Ala 380	c gca gag gag gca a Ala Glu Glu Ala 1385	4420
cta agg aag att co Leu Arg Lys Ile Pr 1390	t gcc atc aac o Ala Ile Asn 1395	cag acc atc act Gln Thr Ile Th	t gaa gcc aat gaa r Glu Ala Asn Glu 1400	4468
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aca gag gcc aag aa Thr Glu Ala Lys As 1420	c aag gcc cat n Lys Ala His 1425	gag gcg gag agg Glu Ala Glu Arg 1430	g atc gca agc gct g Ile Ala Ser Ala 1435	4564
gtc caa aag aat go Val Gln Lys Asn Al 144	a Thr Ser Thr			4612
gca gaa gtt aca ga Ala Glu Val Thr As 1455	p Leu Asp Asn	gag gtg aac aat Glu Val Asn Asn 460	t atg ttg aag caa n Met Leu Lys Gln 1465	4660
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cag gac atg atg at Gln Asp Met Met Me 1485			a Ala Gln Glu Ala	4756
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att att aat gac ct Ile Ile Asn Asp Le 152	u Leu Glu Gln			4852
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gag gag atc atg aag gac att cgc aat ctg gag gac atc agg aag acc 5044 Glu Glu Ile Met Lys Asp Ile Arg Asn Leu Glu Asp Ile Arg Lys Thr 1580 1585 1590 1595	ŀ
tta cca tct ggc tgc ttc aac acc ccg tcc att gaa aag ccc gac tac 5092 Leu Pro Ser Gly Cys Phe Asn Thr Pro Ser Ile Glu Lys Pro Asp Tyr 1600 1605 1610	!
aag gac gac gat gac aag tagtgtettt agggetggaa ggeageatee 5140 Lys Asp Asp Asp Lys 1615	ı
ctctgacagg ggggcagttg tgaggccaca gagtgccttg acacaaagat tacatttttc 5200	ı
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Pro His Leu Gln His Gly Ala Ala Phe Leu Thr Asp Tyr Asn Asn Gln 100 105 110	
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Tyr Pro Ser Ser Ile Asn Leu Thr Leu His Leu Gly Lys Ala Phe Asp 130 135 140	
Ile Thr Tyr Val Arg Leu Lys Phe His Thr Ser Arg Pro Glu Ser Phe	

Ala Ile Tyr Lys Arg Thr Arg Glu Asp Gly Pro Trp Ile Pro Tyr Gln 165 170 170 Tyr Tyr Ser Gly Ser Cys Glu Asn Thr Tyr Ser Lys Ala Asn Arg Gly Phe Ile Arg Thr Gly Gly Asp Glu Gln Gln Ala Leu Cys Thr Asp Glu Phe Ser Asp Ile Ser Pro Leu Thr Gly Gly Asn Val Ala Phe Ser Thr Leu Glu Gly Arg Pro Ser Ala Tyr Asn Phe Asp Asn Ser Pro Val Leu 225 230 235 240 Gln Glu Trp Val Thr Ala Thr Asp Ile Arg Val Thr Leu Asn Arg Leu Asn Thr Phe Gly Asp Glu Val Phe Asn Asp Pro Lys Val Leu Lys Ser 260  $\phantom{\bigg|}265\phantom{\bigg|}$  270 Tyr Tyr Tyr Ala Ile Ser Asp Phe Ala Val Gly Gly Arg Cys Lys Cys 275 280 285 Asn Gly His Ala Ser Glu Cys Met Lys Asn Glu Phe Asp Lys Leu Val 290 295 300 Cys Asn Cys Lys His Asn Thr Tyr Gly Val Asp Cys Glu Lys Cys Leu 305 310 315 320 Pro Phe Phe Asn Asp Arg Pro Trp Arg Arg Ala Thr Ala Glu Ser Ala 325 330 335 Ser Glu Cys Leu Pro Cys Asp Cys Asn Gly Arg Ser Gln Glu Cys Tyr 340 345 350Phe Asp Pro Glu Leu Tyr Arg Ser Thr Gly His Gly Gly His Cys Thr Asn Cys Gln Asp Asn Thr Asp Gly Ala His Cys Glu Arg Cys Arg Glu 370 375 380Asn Phe Phe Arg Leu Gly Asn Asn Glu Ala Cys Ser Ser Cys His Cys 385 390 395 400 Ser Pro Val Gly Ser Leu Ser Thr Gln Cys Asp Ser Tyr Gly Arg Cys 405 410 415 Ser Cys Lys Pro Gly Val Met Gly Asp Lys Cys Asp Arg Cys Gln Pro 420 425 430 Gly Phe His Ser Leu Thr Glu Ala Gly Cys Arg Pro Cys Ser Cys Asp Pro Ser Gly Ser Ile Asp Glu Cys Asn Val Glu Thr Gly Arg Cys Val Cys Lys Asp Asn Val Glu Gly Phe Asn Cys Glu Arg Cys Lys Pro Gly

Phe Phe Asn Leu Glu Ser Ser Asn Pro Arg Gly Cys Thr Pro Cys Phe 485 490 495

- Cys Phe Gly His Ser Ser Val Cys Thr Asn Ala Val Gly Tyr Ser Val 500 510
- Tyr Ser Ile Ser Ser Thr Phe Gln Ile Asp Glu Asp Gly Trp Arg Ala 515 520 525
- Glu Gln Arg Asp Gly Ser Glu Ala Ser Leu Glu Trp Ser Ser Glu Arg 530 535 540
- Gln Asp Ile Ala Val Ile Ser Asp Ser Tyr Phe Pro Arg Tyr Phe Ile 545 550 555 560
- Ala Pro Ala Lys Phe Leu Gly Lys Gln Val Leu Ser Tyr Gly Gln Asn 565 570 575
- Leu Ser Phe Ser Phe Arg Val Asp Arg Arg Asp Thr Arg Leu Ser Ala 580 585 590
- Glu Asp Leu Val Leu Glu Gly Ala Gly Leu Arg Val Ser Val Pro Leu
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- Ile Ala Gln Gly Asn Ser Tyr Pro Ser Glu Thr Thr Val Lys Tyr Val
- Phe Arg Leu His Glu Ala Thr Asp Tyr Pro Trp Arg Pro Ala Leu Thr 625 630 635
- Pro Phe Glu Phe Gln Lys Leu Leu Asn Asn Leu Thr Ser Ile Lys Ile 645 650 655
- Arg Gly Thr Tyr Ser Glu Arg Ser Ala Gly Tyr Leu Asp Asp Val Thr 660 665 670
- Leu Ala Ser Ala Arg Pro Gly Pro Gly Val Pro Ala Thr Trp Val Glu 675 680 685
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- Cys Val Leu Cys Ala Cys Asn Gly His Ser Glu Thr Cys Asp Pro Glu
  725 730 735
- Thr Gly Val Cys Asn Cys Arg Asp Asn Thr Ala Gly Pro His Cys Glu 740 745 750
- Lys Cys Ser Asp Gly Tyr Tyr Gly Asp Ser Thr Ala Gly Thr Ser Ser 755 760 765
- Asp Cys Gln Pro Cys Pro Cys Pro Gly Gly Ser Ser Cys Ala Val Val 770 785
- Pro Lys Thr Lys Glu Val Val Cys Thr Asn Cys Pro Thr Gly Thr Thr 785 790 795 800
- Gly Lys Arg Cys Glu Leu Cys Asp Asp Gly Tyr Phe Gly Asp Pro Leu

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- 820 825 830
- Asn Ile Asp Pro Asn Ala Val Gly Asn Cys Asn Arg Leu Thr Gly Glu 835 840 845
- Cys Leu Lys Cys Ile Tyr Asn Thr Ala Gly Phe Tyr Cys Asp Arg Cys 850 855 860
- Lys Asp Gly Phe Phe Gly Asn Pro Leu Ala Pro Asn Pro Ala Asp Lys 865 870 875 880
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- Ser Cys Asn Pro Val Thr Gly Gln Cys Glu Cys Leu Pro His Val Thr 900 905 910
- Gly Gln Asp Cys Gly Ala Cys Asp Pro Gly Phe Tyr Asn Leu Gln Ser 915 920 925
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- Pro Glu Gly Cys Lys Pro Cys Asp Cys His Pro Glu Gly Ser Leu Ser 980 985 990
- Leu Gln Cys Lys Asp Asp Gly Arg Cys Glu Cys Arg Glu Gly Phe Val 995 1000 1005
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- Trp Pro Gly Cys Gln Glu Cys Pro Ala Cys Tyr Arg Leu Val Lys Asp 025 1030 1035 1040
- Lys Val Ala Asp His Arg Val Lys Leu Gln Glu Leu Glu Ser Leu Ile 1045 1050 1055
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- Arg Val Asn Asn Thr Leu Ser Ser Gln Ile Ser Arg Leu Gln Asn Ile 105 1110 1115 1120
- Arg Asn Thr Ile Glu Glu Thr Gly Asn Leu Ala Glu Gln Ala Arg Ala 1125 1130 1135

His Val Glu Asn Thr Glu Arg Leu Ile Glu Ile Ala Ser Arg Glu Leu 1140 1145 1150

- Glu Lys Ala Lys Val Ala Ala Ala Asn Val Ser Val Thr Gln Pro Glu 1155 1160 1165
- Ser Thr Gly Asp Pro Asn Asn Met Thr Leu Leu Ala Glu Glu Ala Arg 1170 1175 1180
- Lys Leu Ala Glu Arg His Lys Gln Glu Ala Asp Asp Ile Val Arg Val 185 1190 1195 1200
- Ala Lys Thr Ala Asn Asp Thr Ser Thr Glu Ala Tyr Asn Leu Leu 1205 1210 1215
- Arg Thr Leu Ala Gly Glu Asn Gln Thr Ala Phe Glu Ile Glu Glu Leu 1220 1225 1230
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- Gln Ala Ala Arg Val His Glu Glu Ala Lys Arg Ala Gly Asp Lys Ala 1250 1255 1260
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- Thr Leu Glu Asn Glu Ala Asn Asn Ile Lys Met Glu Ala Glu Asn Leu 1285 1290 1295
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- Lys Thr Glu Gln Gln Thr Ala Asp Gln Leu Leu Ala Arg Ala Asp Ala 1330 1335 1340
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- Ala Ile Asn Gln Thr Ile Thr Glu Ala Asn Glu Lys Thr Arg Glu Ala 1395 1400 1405
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- Lys Ala His Glu Ala Glu Arg Ile Ala Ser Ala Val Gln Lys Asn Ala 425 1430 1435 1440
- Thr Ser Thr Lys Ala Glu Ala Glu Arg Thr Phe Ala Glu Val Thr Asp 1445 1450 1455

Leu Asp Asn Glu Val Asn Asn Met Leu Lys Gln Leu Gln Glu Ala Glu 1465 Lys Glu Leu Lys Arg Lys Gln Asp Asp Ala Asp Gln Asp Met Met 1480 1485 Ala Gly Met Ala Ser Gln Ala Ala Gln Glu Ala Glu Ile Asn Ala Arg 1495 1500 Lys Ala Lys Asn Ser Val Thr Ser Leu Leu Ser Ile Ile Asn Asp Leu 1510 1515 Leu Glu Gln Leu Gly Gln Leu Asp Thr Val Asp Leu Asn Lys Leu Asn Glu Ile Glu Gly Thr Leu Asn Lys Ala Lys Asp Glu Met Lys Val Ser 1545 Asp Leu Asp Arg Lys Val Ser Asp Leu Glu Asn Glu Ala Lys Lys Gln 1560 Glu Ala Ala Ile Met Asp Tyr Asn Arg Asp Ile Glu Glu Ile Met Lys Asp Ile Arg Asn Leu Glu Asp Ile Arg Lys Thr Leu Pro Ser Gly Cys 1590 1595 Phe Asn Thr Pro Ser Ile Glu Lys Pro Asp Tyr Lys Asp Asp Asp Asp 1610 Lys <210> 27 <211> 4972 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)..(4752) <220> <221> misc\_feature <222> (4729)..(4752) cag gca gcc atg gac gag tgc acg gac gag ggc ggg cgg ccg cag cgc Gln Ala Ala Met Asp Glu Cys Thr Asp Glu Gly Gly Arg Pro Gln Arg tgc atg ccc gag ttc gtc aac gcc gct ttc aac gtg act gtg gtg gcc Cys Met Pro Glu Phe Val Asn Ala Ala Phe Asn Val Thr Val Val Ala 25

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gtg acc ggg gtc acc aag tcc tgt cac ctg tgc gac gcc ggg cag ccc

Val	Thr 50	Gly	Val	Thr	Lys	Ser 55	Сув	His	Leu	Сув	Asp 60	Ala	Gly	Gln	Pro	
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gac Asp	acc Thr	acc Thr	tgg Trp	tgg Trp 85	caa Gln	agc Ser	cag Gln	acc Thr	atg Met 90	ctg Leu	gcc Ala	61 y 999	gtg Val	cag Gln 95	tac Tyr	288
			atc Ile 100													336
			cgt Arg													384
			cgc Arg													432
			tcc Ser													480
			gga Gly													528
			tct Ser 180													576
			ccc Pro													624
			act Thr													672
			gat Asp													720
			atc Ile													768
			agc Ser 260													816
			cat His													864
			gac										agt Ser			912

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cct Pro	gtg Val 370	ggc Gly	tct Ser	cta Leu	agc Ser	aca Thr 375	cag Gln	tgt Cys	gat Asp	agt Ser	tac Tyr 380	ggc Gly	aga Arg	tgc Cys	agc Ser	1152
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		agc Ser														1296
		aat Asn 435														1344
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		gat Asp														1536
		gcc Ala 515														1584
		aag Lys														1632

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	ctc Leu															1824
	gaa Glu 610															1872
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	agt Ser															1968
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	gtt Val															2160
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	aca Thr															2304
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gtt gc Val Al	a Āsp			Val					Leu						3072
aac ct	gga	act	999	gat	gag	atg	gtg	aca	gat	caa	gcc	ttc	gag	gat	3120

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aag aca gcc aat gat acg tca act gag gca tac aac ctg ctt ctg agg Lys Thr Ala Asn Asp Thr Ser Thr Glu Ala Tyr Asn Leu Leu Leu Arg 1170 1175 1180  aca ctg gca gga gaa aat caa aca gca ttt gag att gaa gag ctt aat Thr Leu Ala Gly Glu Asn Gln Thr Ala Phe Glu Ile Glu Glu Leu Asn 1185 1190 1195 1200  agg aag tat gaa caa gcg aag aac atc tca cag gat ctg gaa aaa caa Arg Lys Tyr Glu Gln Ala Lys Asn Ile Ser Gln Asp Leu Glu Lys Gln 1205 1210 1215  gct gcc cga gta cat gag gag gcc aaa agg gcc ggt gac aaa gct gtg Ala Ala Arg Val His Glu Glu Ala Lys Arg Ala Gly Asp Lys Ala Val 1220 1225 1230  gag atc tat gcc agc gtg gct cag ctg agc cct ttg gac tct gag aca Glu Ile Tyr Ala Ser Val Ala Gln Leu Ser Pro Leu Asp Ser Glu Thr 1235 1240 1245	3600 3648
aag aca gcc aat gat acg tca act gag gca tac aac ctg ctt ctg agg Lys Thr Ala Asn Asp Thr Ser Thr Glu Ala Tyr Asn Leu Leu Leu Arg 1170 1175 1180  aca ctg gca gga gaa aat caa aca gca ttt gag att gaa gag ctt aat Thr Leu Ala Gly Glu Asn Gln Thr Ala Phe Glu Ile Glu Glu Leu Asn 1185 1190 1195 1200  agg aag tat gaa caa gcg aag aac atc tca cag gat ctg gaa aaa caa Arg Lys Tyr Glu Gln Ala Lys Asn Ile Ser Gln Asp Leu Glu Lys Gln 1205 1210 1215  gct gcc cga gta cat gag gag gcc aaa agg gcc ggt gac aaa gct gtg Ala Ala Arg Val His Glu Glu Ala Lys Arg Ala Gly Asp Lys Ala Val 1220 1225 1230  gag atc tat gcc agc gtg gct cag ctg agc cct ttg gac tct gag aca Glu Ile Tyr Ala Ser Val Ala Gln Leu Ser Pro Leu Asp Ser Glu Thr	3600 3648 3696

1265	1270	1275	1280	
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		a ctc cta gcc cga n Leu Leu Ala Arg 1305		6
aag gcc ctc gct Lys Ala Leu Ala 1315	gaa gaa gct gc Glu Glu Ala Al 132	a aag aag gga cgg a Lys Lys Gly Arg 0	gat acc tta caa 398 Asp Thr Leu Gln 1325	4
		c ctg aaa gat ttt n Leu Lys Asp Phe 1340		2
		g gag gca cta agg u Glu Ala Leu Arg 1355		0
Ile Asn Gln Thr		c aat gaa aag acc a Asn Glu Lys Thr 1370		8
		g gat gcc aca gag a Asp Ala Thr Glu 1385		6
		a agc gct gtc caa a Ser Ala Val Gln O		4
		a act ttt gca gaa g Thr Phe Ala Glu 1420		2
		g aag caa ctg cag u Lys Gln Leu Gln 1435		0
Glu Leu Lys Arg		c gct gac cag gac p Ala Asp Gln Asp 1450		8
		a gaa gcc gag atc n Glu Ala Glu Ile 1465		6
		c ctc agc att att u Leu Ser Ile Ile 0		4
		a gtg gac ctg aat r Val Asp Leu Asn 1500		.2
		c aaa gat gaa atg a Lys Asp Glu Met 1515		0

Leu Asp Arg Lys Val Ser Asp Leu Glu Asn Glu Ala Lys Lys Gln Glu 1525 1530 1535	4608												
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Asn Thr Pro Ser Ile Glu Lys Pro Asp Tyr Lys Asp Asp Asp Asp Lys 1570 1575 1580	4752												
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20 25 30  Thr Asn Thr Cys Gly Thr Pro Pro Glu Glu Tyr Cys Val Gln Thr Gly													
20 25 30  Thr Asn Thr Cys Gly Thr Pro Pro Glu Glu Tyr Cys Val Gln Thr Gly 35 40 45  Val Thr Gly Val Thr Lys Ser Cys His Leu Cys Asp Ala Gly Gln Pro													
Thr Asn Thr Cys Gly Thr Pro Pro Glu Glu Tyr Cys Val Gln Thr Gly 35 40 45  Val Thr Gly Val Thr Lys Ser Cys His Leu Cys Asp Ala Gly Gln Pro 50 55 60  His Leu Gln His Gly Ala Ala Phe Leu Thr Asp Tyr Asn Asn Gln Ala													
Thr Asn Thr Cys Gly Thr Pro Pro Glu Glu Tyr Cys Val Gln Thr Gly 35  Val Thr Gly Val Thr Lys Ser Cys His Leu Cys Asp Ala Gly Gln Pro 50  His Leu Gln His Gly Ala Ala Phe Leu Thr Asp Tyr Asn Asn Gln Ala 65  Asp Thr Thr Trp Trp Gln Ser Gln Thr Met Leu Ala Gly Val Gln Tyr													
Thr Asn Thr Cys Gly Thr Pro Pro Glu Glu Tyr Cys Val Gln Thr Gly 40  Val Thr Gly Val Thr Lys Ser Cys His Leu Cys Asp Ala Gly Gln Pro 50  His Leu Gln His Gly Ala Ala Phe Leu Thr Asp Tyr Asn Asn Gln Ala 65  Asp Thr Thr Trp Trp Gln Ser Gln Thr Met Leu Ala Gly Val Gln Tyr 90  Pro Ser Ser Ile Asn Leu Thr Leu His Leu Gly Lys Ala Phe Asp Ile													
Thr Asn Thr Cys Gly Thr Pro Pro Glu Glu Tyr Cys Val Gln Thr Gly 40  Val Thr Gly Val Thr Lys Ser Cys His Leu Cys Asp Ala Gly Gln Pro 50  His Leu Gln His Gly Ala Ala Phe Leu Thr Asp Tyr Asn Asn Gln Ala 65  Asp Thr Thr Trp Trp Gln Ser Gln Thr Met Leu Ala Gly Val Gln Tyr 95  Pro Ser Ser Ile Asn Leu Thr Leu His Leu Gly Lys Ala Phe Asp Ile 100  Thr Tyr Val Arg Leu Lys Phe His Thr Ser Arg Pro Glu Ser Phe Ala													

Ile	Arg	Thr	Gly	Gly 165	Asp	Glu	Gln	Gln	Ala 170	Leu	Cys	Thr	Дар	Glu 175	Phe
Ser	Asp	Ile	Ser 180	Pro	Leu	Thr	Gly	Gly 185	Asn	Val	Ala	Phe	Ser 190	Thr	Leu
Glu	Gly	Arg 195	Pro	Ser	Ala	Tyr	Asn 200	Phe	Asp	Asn	Ser	Pro 205	Val	Leu	Gln
	210				Thr	215					220				
225					Val 230					235					240
				245	Asp				250					255	
			260		Сув			265					270		
Asn	Cys	Lys 275	His	Asn	Thr	Tyr	Gly 280	Val	Asp	Сув	Glu	Lys 285	Сув	Leu	Pro
Phe	Phe 290	Asn	Asp	Arg	Pro	Trp 295	Arg	Arg	Ala	Thr	Ala 300	Glu	Ser	Ala	Ser
Glu 305	Сув	Leu	Pro	Сув	Asp 310	Сув	Asn	Gly	Arg	Ser 315	Gln	Glu	Сув	Tyr	Phe 320
				325	Arg				330	-	-		-	335	
			340		Asp			345					350		
		355			Asn		360	٠				<b>36</b> 5			
	370				Ser	375					380	_	_	•	
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Phe	His	Ser	Leu	Thr 405	Glu	Ala	Gly	Сув	Arg 410	Pro	Сув	Ser	Сув	Asp 415	Pro
Ser	Gly	Ser	11e 420	qaA	Glu	Cys	Asn	Val 425	Glu	Thr	Gly	Arg	Сув 430	Val	Сув
Lys	Asp	Asn 435	Val	Glu	Gly	Phe	Asn 440	Сув	Glu	Arg	Сув	Lув 445	Pro	Gly	Phe
Phe	Asn 450	Leu	Glu	Ser	Ser	Asn 455	Pro	Arg	Gly	Сув	Thr 460	Pro	Сув	Phe	Суз
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Ser Ile Ser Ser Thr Phe Gln Ile Asp Glu Asp Gly Trp Arg Ala Glu
485 490 495

- Gln Arg Asp Gly Ser Glu Ala Ser Leu Glu Trp Ser Ser Glu Arg Gln 500 505 510
- Asp Ile Ala Val Ile Ser Asp Ser Tyr Phe Pro Arg Tyr Phe Ile Ala 515 520 525
- Pro Ala Lys Phe Leu Gly Lys Gln Val Leu Ser Tyr Gly Gln Asn Leu 530 535 540
- Ser Phe Ser Phe Arg Val Asp Arg Arg Asp Thr Arg Leu Ser Ala Glu 545 550 555 560
- Asp Leu Val Leu Glu Gly Ala Gly Leu Arg Val Ser Val Pro Leu Ile 565 570 575
- Ala Gln Gly Asn Ser Tyr Pro Ser Glu Thr Thr Val Lys Tyr Val Phe 580 585 590
- Arg Leu His Glu Ala Thr Asp Tyr Pro Trp Arg Pro Ala Leu Thr Pro
  595 600 605
- Phe Glu Phe Gln Lys Leu Leu Asn Asn Leu Thr Ser Ile Lys Ile Arg
- Gly Thr Tyr Ser Glu Arg Ser Ala Gly Tyr Leu Asp Asp Val Thr Leu 625 630 635 640
- Ala Ser Ala Arg Pro Gly Pro Gly Val Pro Ala Thr Trp Val Glu Ser 645 650 655
- Cys Thr Cys Pro Val Gly Tyr Gly Gly Gln Phe Cys Glu Met Cys Leu 660 665 670
- Ser Gly Tyr Arg Arg Glu Thr Pro Asn Leu Gly Pro Tyr Ser Pro Cys 675 680 685
- Val Leu Cys Ala Cys Asn Gly His Ser Glu Thr Cys Asp Pro Glu Thr 690 695 700
- Gly Val Cys Asn Cys Arg Asp Asn Thr Ala Gly Pro His Cys Glu Lys 705 710 715 720
- Cys Ser Asp Gly Tyr Tyr Gly Asp Ser Thr Ala Gly Thr Ser Ser Asp 725 730 735
- Cys Gln Pro Cys Pro Cys Pro Gly Gly Ser Ser Cys Ala Val Val Pro 740  $\phantom{-}745\phantom{0}$  750
- Lys Thr Lys Glu Val Val Cys Thr Asn Cys Pro Thr Gly Thr Thr Gly 755  $\phantom{000}760\phantom{000}$  765
- Lys Arg Cys Glu Leu Cys Asp Asp Gly Tyr Phe Gly Asp Pro Leu Gly 770 780
- Arg Asn Gly Pro Val Arg Leu Cys Arg Leu Cys Gln Cys Ser Asp Asn 785 790 795 800
- Ile Asp Pro Asn Ala Val Gly Asn Cys Asn Arg Leu Thr Gly Glu Cys

				805					810					815	
Leu	Lув	Сув	Ile 820	Tyr	Asn	Thr	Ala	Gly 825	Phe	Tyr	Сув	Ąsp	Arg 830		Lys
Asp	Gly	Phe 835	Phe	Gly	Asn	Pro	Leu 840	Ala	Pro	Asn	Pro	Ala 845	Asp	Lys	Суз
ьув	Ala 850	Сув	Asn	Cys	Asn	Pro 855	Tyr	Gly	Thr	Met	Lys 860	Gln	Gln	Ser	Ser
Cys 865	Asn	Pro	Val	Thr	Gly 870	Gln	Сув	Glu	Сув	Leu 875	Pro	Bis	Val	Thr	Gly 880
Gln	Asp	Сув	Gly	<b>Ala</b> 885	Суз	Asp	Pro	Gly	Phe 890	Tyr	Asn	Leu	Gln	Ser 895	Gly
Gln	Gly	Суз	Glu 900	Arg	Сув	Asp	Суз	His 905	Ala	Leu	Gly	Ser	Thr 910	Asn	Gly
Gln	Сув	<b>А</b> БР 915	Ile	Arg	Thr	Gly	Gln 920		Glu	Сув	Gln	Pro 925	Gly	Ile	Thr
Gly	Gln 930	His	Сув	Glu	Arg	Сув 935	Glu	Val	Asn	His	Phe 940	Gly	Phe	Gly	Pro
Glu 945	Gly	Сув	Lys	Pro	Сув 950	Asp	Сув	His	Pro	Glu 955		Ser	Leu	Ser	Leu 960
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Asn	Arg	Сув	Asp 980	Gln	Cys	Glu	Glu	Asn 985	Tyr	Phe	Tyr	Asn	Arg 990	Ser	Trp
Pro	Gly	Сув 995	Gln <sup>.</sup>	Glu	Сув		Ala 1000	Суз	Tyr	Arg		Val 1005	Lys	Asp	Lys
	Ala 1010	Asp	His	Arg		Lys 1015	Leu	Gln	Glu		Glu 1020	Ser	Leu	Ile	Ala
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Arg	Leu	Lys	Glu 1	Ala 1045	Glu	Arg	Glu		Met 1050	Asp	Leu	Leu		Glu 1055	Ala
Gln	Asp		Г0 <b>6</b> 0	Asp	Val	Yab		Asn 1065	Leu	Met	Asp		Leu 1070	Gln	Arg
Val		Asn 075	Thr	Leu	Ser		Gln 1080	Ile	Ser	Arg		Gln 085	Asn	Ile	Arg
Asn 1	Thr .090	Ile	Glu	Glu		Gly .095	Asn	Leu	Ala		Gln 1100	Ala	Arg	Ala	His
Val		Asn	Thr		Arg		Ile	Glu	Ile	Ala		Arg	Glu		Glu

Lys Ala Lys Val Ala Ala Ala Asn Val Ser Val Thr Gln Pro Glu Ser 1125 1130 1135

Thr Gly Asp Pro Asn Asn Met Thr Leu Leu Ala Glu Glu Ala Arg Lys 1140 1145 1150

- Leu Ala Glu Arg His Lys Gln Glu Ala Asp Asp Ile Val Arg Val Ala 1155 1160 1165
- Lys Thr Ala Asn Asp Thr Ser Thr Glu Ala Tyr Asn Leu Leu Leu Arg 1170 1175 1180
- Thr Leu Ala Gly Glu Asn Gln Thr Ala Phe Glu Ile Glu Glu Leu Asn 1185 1190 1195 1200
- Arg Lys Tyr Glu Gln Ala Lys Asn Ile Ser Gln Asp Leu Glu Lys Gln 1205 1210 1215
- Ala Ala Arg Val His Glu Glu Ala Lys Arg Ala Gly Asp Lys Ala Val 1220 1225 1230
- Glu Ile Tyr Ala Ser Val Ala Gln Leu Ser Pro Leu Asp Ser Glu Thr 1235 1240 1245
- Leu Glu Asn Glu Ala Asn Asn Ile Lys Met Glu Ala Glu Asn Leu Glu 1250 1255 1260
- Gln Leu Ile Asp Gln Lys Leu Lys Asp Tyr Glu Asp Leu Arg Glu Asp 1265 1270 1275 1280
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- Thr Glu Gln Gln Thr Ala Asp Gln Leu Leu Ala Arg Ala Asp Ala Ala 1300 1305 1310
- Lys Ala Leu Ala Glu Glu Ala Ala Lys Lys Gly Arg Asp Thr Leu Gln 1315 1320 1325
- Glu Ala Asn Asp Ile Leu Asn Asn Leu Lys Asp Phe Asp Arg Arg Val 1330 1340
- Asn Asp Asn Lys Thr Ala Ala Glu Glu Ala Leu Arg Lys Ile Pro Ala 1345 1350 1355 1360
- Ile Asn Gln Thr Ile Thr Glu Ala Asn Glu Lys Thr Arg Glu Ala Gln
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- Gln Ala Leu Gly Ser Ala Ala Ala Asp Ala Thr Glu Ala Lys Asn Lys 1380 1385 1390
- Ala His Glu Ala Glu Arg Ile Ala Ser Ala Val Gln Lys Asn Ala Thr 1395 1400 1405
- Ser Thr Lys Ala Glu Ala Glu Arg Thr Phe Ala Glu Val Thr Asp Leu 1410 1415 1420
- Asp Asn Glu Val Asn Asn Met Leu Lys Gln Leu Gln Glu Ala Glu Lys 1425 1430 1435 1440
- Glu Leu Lys Arg Lys Gln Asp Asp Ala Asp Gln Asp Met Met Ala 1445 1450 1455

Gly Met Ala Ser Gln Ala Ala Gln Glu Ala Glu Ile Asn Ala Arg Lys 1460 1465 1470

- Ala Lys Asn Ser Val Thr Ser Leu Leu Ser Ile Ile Asn Asp Leu Leu 1475 1480 1485
- Glu Gln Leu Gly Gln Leu Asp Thr Val Asp Leu Asn Lys Leu Asn Glu 1490 1495 1500
- Ile Glu Gly Thr Leu Asn Lys Ala Lys Asp Glu Met Lys Val Ser Asp 1505 1510 1515 1520
- Leu Asp Arg Lys Val Ser Asp Leu Glu Asn Glu Ala Lys Lys Gln Glu 1525 1530 1535
- Ala Ala Ile Met Asp Tyr Asn Arg Asp Ile Glu Glu Ile Met Lys Asp 1540 1540 1550
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- ggcctcggga tacgccgcta ggcgagtgca gcgcggcacc ccagcctttg ccgaggggcc 180
- cgccgcagcg gg atg acg ggc ggc ggg cgg gcc gcg ctg gcc ctg cag ccc 231

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  Arg Gly Arg Leu Trp Pro Leu Leu Ala Val Leu Ala Ala Val Ala Gly
  15 20 25
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  Cys Val Arg Ala Ala Met Asp Glu Cys Ala Asp Glu Gly Gly Arg Pro
  30 35 40 45
- cag cgc tgc atg ccg gag ttt gtt aat gcc gcc ttc aat gtg acc gtg
  Gln Arg Cys Met Pro Glu Phe Val Asn Ala Ala Phe Asn Val Thr Val
  50 55 60

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act Thr	Gly 999	gtg Val 80	acc Thr	gga Gly	gtc Val	act Thr	aag Lys 85	tcc Ser	tgt Cys	cac His	ctg Leu	tgc Cys 90	gac Asp	gcc Ala	ggc Gly	471
cag Gln	cag Gln 95	cac His	ctg Leu	caa Gln	cac His	100 GJA 333	gca Ala	gcc Ala	ttc Phe	ctg Leu	acc Thr 105	gac Asp	tac Tyr	aac Asn	aac Asn	519
cag Gln 110	gcc Ala	gac Asp	acc Thr	acc Thr	tgg Trp 115	tgg Trp	caa Gln	agc Ser	cag Gln	act Thr 120	atg Met	ctg Leu	gcc Ala	ggg ggg	gtg Val 125	567
Gln	Tyr	Pro	Asn	tcc Ser 130	Ile	Asn	Leu	Thr	Leu 135	His	Leu	Gly	Lys	Ala 140	Phe	615
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				gga Gly												999
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				gcc Ala 290												1095
atg	tgc	aac	tgc	aaa	cat	aac	aca	tac	<b>g</b> ga	gtt	gac	tgt	gaa	aag	tgc	1143

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acc Thr	aac Asn	tgc Cys	cgg Arg	gat Asp 370	aac Asn	aca Thr	gat Asp	ggt Gly	gcc Ala 375	aag Lys	tgc Cys	gag Glu	agg Arg	tgc Cys 380	cgg Arg	1335
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tgc Cys	agc Ser	cct Pro 400	gtt Val	ggt Gly	tct Ser	ctc Leu	agc Ser 405	aca Thr	cag Gln	tgt Cys	gac Asp	agt Ser 410	tac Tyr	ggc Gly	aga Arg	1431
tgc Cys	agc Ser 415	tgt Cys	aag Lys	cca Pro	gga Gly	gtg Val 420	atg Met	ggt Gly	gac Asp	aag Lys	tgt Cys 425	gac Asp	cgt Arg	tgt Cys	cag Gln	1479
cct Pro 430	ggg Gly	ttc Phe	cat His	tcc Ser	ctc Leu 435	act Thr	gag Glu	gca Ala	gga Gly	tgc Cys 440	agg Arg	cca Pro	tgc Cys	tcc Ser	tgc Cys 445	1527
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gtt Val	tgc Cys	aaa Lys	gac Asp 465	aat Asn	gtt Val	gaa Glu	ggc Gly	ttc Phe 470	aac Asn	tgt Cys	gag Glu	aga Arg	tgc Cys 475	aaa Lys	cct Pro	1623
gga Gly	ttt Phe	ttt Phe 480	aat Asn	ctg Leu	gag Glu	tca Ser	tct Ser 485	aat Asn	cct Pro	aag Lys	ggc Gly	tgc Cys 490	aca Thr	ccc Pro	tgc Cys	1671
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gtt Val 510	tat Tyr	gac Asp	atc Ile	tcc Ser	tcc Ser 515	acc Thr	ttt Phe	cag Gln	att Ile	gat Asp 520	gag Glu	gat Asp	gly ggg	tgg Trp	cgc Arg 525	1767
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2583

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acc ctg gca gga Thr Leu Ala Gly 1215				•
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gag atc tat gcc Glu Ile Tyr Ala 1265	Ser Val Ala Gln	ctg acc cct gtg Leu Thr Pro Val 270	gac tet gag gec 4023 Asp Ser Glu Ala 1275	į.
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Asn					Ala					Leu				ccc Pro		4359
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Thr	Thr	Trp 115	Trp	Gln	Ser	Gln	Thr 120	Met	Leu	Ala	Gly	Val 125	Gln	Tyr	Pro
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Cys Asp Gln Cys Glu Glu Asn Tyr Phe Tyr Asn Arg Ser Trp Pro Gly

1010 1015 1020

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	gat Asp															720

gca Ala	atc Ile	tca Ser	gac Asp	ttt Phe 245	gct Ala	gtg Val	ggc Gly	ggc Gly	agg Arg 250	tgt Cys	aaa Lys	tgt Cys	aac Asn	gga Gly 255	cat His	768
gcc Ala	agc Ser	gag Glu	tgt Cys 260	gta Val	aag Lys	aac Asn	gag Glu	ttt Phe 265	gac Asp	aaa Lys	ctc Leu	atg Met	tgc Cys 270	aac Asn	tgc Cys	816
ааа Lув	cat His	aac Asn 275	aca Thr	tac Tyr	gga Gly	gtt Val	gac Asp 280	tgt Cys	gaa Glu	aag Lys	tgc Cys	ctg Leu 285	cct Pro	ttc Phe	ttc Phe	864
aat Asn	gac Asp 290	cgg Arg	ccg Pro	tgg Trp	agg Arg	agg Arg 295	gcg Ala	act Thr	gct Ala	gag Glu	agc Ser 300	gcc Ala	agc Ser	gag Glu	tgc Cys	912
ctt Leu 305	cct Pro	tgt Cys	gac Asp	tgc Cys	aat Asn 310	ggc	cga Arg	tcc Ser	caa Gln	gag Glu 315	tgc Cys	tac Tyr	ttt Phe	gat Asp	cct Pro 320	960
gaa Glu	cta Leu	tac Tyr	cgt Arg	tcc Ser 325	act Thr	gga Gly	cat His	ggt Gly	ggc Gly 330	cac His	tgt Cys	acc Thr	aac Asn	tgc Cys 335	cgg Arg	1008
gat Asp	aac Asn	aca Thr	gat Asp 340	ggt	gcc Ala	aag Lys	tgc Cys	gag Glu 345	agg <b>Ar</b> g	tgc Cys	cgg Arg	gag Glu	aat Asn 350	ttc Phe	ttc Phe	1056
cgc Arg	ctg Leu	ggg Gly 355	aac Asn	act Thr	gaa Glu	gcc Ala	tgc Cys 360	tct Ser	ccg Pro	tgc Cys	cac His	tgc Cys 365	agc Ser	cct Pro	gtt Val	1104
					cag Gln											1152
cca Pro 385	gga Gly	gtg Val	atg Met	ggt Gly	gac Asp 390	aag Lys	tgt Cys	gac Asp	cgt Arg	tgt Cys 395	cag Gln	cct Pro	gjà aaa	ttc Phe	cat His 400	1200
					gga Gly											1248
agc Ser	aca Thr	gac Asp	gag Glu 420	tgt Cys	aat Asn	gtt Val	gaa Glu	aca Thr 425	gga Gly	aga Arg	tgc Cys	gtt Val	tgc Cys 430	aaa Lys	gac Asp	1296
					aac Asn											1344
					cct Pro											1392
					aca Thr 470											1440

tcc tcc acc Ser Ser Th	ttt cag r Phe Gln 485	att gat Ile Asp	gag gat Glu Asp	ggg Gly 490	tgg Trp	cgc Arg	gtg Val	gag Glu	cag Gln 495	aga Arg	1488
gat ggc tcg Asp Gly Se	g gag gcg r Glu Ala 500	tct ctg Ser Leu	gag tgg Glu Trp 505	Ser	tca Ser	gac Asp	agg Arg	caa Gln 510	tat Tyr	att Ile	1536
gcc gta ato Ala Val Ile 51!	e Ser Asp	agt tac Ser Tyr	ttt cct Phe Pro 520	aga Arg	tac Tyr	ttc Phe	atc Ile 525	gcc Ala	cct Pro	gtg Val	1584
aag ttc ctg Lys Phe Let 530	g ggc aac 1 Gly Asn	cag gtc Gln Val 535	ctg agt Leu Ser	tat Tyr	Gly aaa	cag Gln 540	aat Asn	ctt Leu	tcc Ser	ttc Phe	1632
tcc ttc cga Ser Phe Arg 545											1680
gtg ctc gaa Val Leu Glu											1728
ggc aac too Gly Asn Sen				Val							1776
cat gaa gca His Glu Ala 599	a Thr Asp										1824
ttt cag aag Phe Gln Ly: 610											1872
tac agc gag Tyr Ser Glu 625	g agg agc ı Arg Ser	gct ggg Ala Gly 630	tac ttg Tyr Leu	gat Asp	gat Asp 635	gtc Val	acc Thr	ttg Leu	caa Gln	agt Ser 640	1920
get ege eet Ala Arg Pro											1968
tgt cca gtg Cys Pro Val				Сув							2016
tac aga aga Tyr Arg Arg 67!	g Glu Thr										2064
tgt acc tgr Cys Thr Cyr 690											2112
tgt gac tgo Cys Asp Cyo 705											2160
gat ggg ta	c tat ggg	gac tca	acc cts	ggc	acc	tcc	tct	gac	tgc	cag	2208

Asp	Gly	Tyr	Tyr	Gly 725	Asp	Ser	Thr	Leu	Gly 730	Thr	Ser	Ser	Asp	Cys 735	Gln	
cct Pro	tgt Cys	ccc Pro	tgc Cys 740	ccc Pro	ggt Gly	ggè.	tca Ser	agt Ser 745	tgt Cys	gcc Ala	att Ile	gtc Val	cca Pro 750	aag Lys	aca Thr	2256
aag Lys	gaa Glu	gtg Val 755	gtg Val	tgc Cys	acg Thr	cac His	tgt Cys 760	ccg Pro	act Thr	ggc Gly	act Thr	gcc Ala 765	ggc Gly	aag Lys	aga Arg	2304
tgt Cys	gaa Glu 770	ctc Leu	tgt Cys	gat Asp	gac Asp	ggc Gly 775	tac Tyr	ttt Phe	gga Gly	gac Asp	cct Pro 780	ctg Leu	ggc Gly	agc Ser	aat Asn	2352
	ccc Pro															2400
	aac Asn															2448
	atc Ile															2496
	ttc Phe															2544
	gcc Ala 850															2592
	acc Thr															2640
	act Thr															2688
	agg Arg															2736
	cgc Arg															2784
	gag Glu 930															2832
	cct Pro															2880
	gac Asp															2928

:

	965	970	975
gac cag tgt Asp Gln Cys	gaa gag aac tat Glu Glu Asn Tyr 980	tte tac aat cgg tcc Phe Tyr Asn Arg Ser 985	tgg cct ggc tgc 2976 Trp Pro Gly Cys 990
cag gag tgt Gln Glu Cys 995	Pro Ala Cys Tyr	cga ctt gtg aag gat Arg Leu Val Lys Asp .000	aag get get gag 3024 Lys Ala Ala Glu 005
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gaa gca gaa Glu Ala Glu	agg gag gtg aca Arg Glu Val Thr 1045	gac ctt ctc cgt gag Asp Leu Leu Arg Glu 1050	gct cag gaa gtc 3168 Ala Gln Glu Val 1055
Lys Asp Val	gat caa aat ctg Asp Gln Asn Leu 1060	atg gat cgc ctt cag Met Asp Arg Leu Gln 1065	aga gta aat agc 3216 Arg Val Asn Ser 1070
agc ctg cat Ser Leu His 1075	Ser Gln Ile Ser	cga ctg cag aat atc Arg Leu Gln Asn Ile 080 1	cgg aat act atc 3264 Arg Asn Thr Ile 085
gaa gag acc Glu Glu Thr 1090	ggg atc ttg gct Gly Ile Leu Ala 1095	gag cga gca cgg tcc Glu Arg Ala Arg Ser 1100	cga gtg gag agt 3312 Arg Val Glu Ser
aca gag cag Thr Glu Gln 1105	ctg att gag atc Leu Ile Glu Ile 1110	gcc tcc agg gag ctc Ala Ser Arg Glu Leu 1115	gag aaa gca aaa 3360 Slu Lys Ala Lys 1120
atg gcc gcc Met Ala Ala	aat gtg tca atc Asn Val Ser Ile 1125	act cag cca gag tct Thr Gln Pro Glu Ser 1130	aca ggg gag cca 3408 Thr Gly Glu Pro 1135
Asn Asn Met	acc ctc ttg gca Thr Leu Leu Ala 140	gaa gaa gcc cga agg Glu Glu Ala Arg Arg : 1145	ett gca gag cgt 3456 Leu Ala Glu Arg 1150
cat aaa cag His Lys Gln 1155	Glu Ala Asp Asp	att gta cga gtg gca : Ile Val Arg Val Ala : 160 1:	aag aca gcc aac 3504 Lys Thr Ala Asn L65
gag act tca Glu Thr Ser 1170	gct gag gca tat Ala Glu Ala Tyr 1175	aat ctg ctt ttg agg : Asn Leu Leu Leu Arg ! 1180	acc ctg gca gga 3552 Thr Leu Ala Gly
gaa aat caa Glu Asn Gln 1185	act gcg ctg gag a Thr Ala Leu Glu i 1190	att gaa gaa ctt aac ( Ile Glu Glu Leu Asn ) 1195	ngg aag tac gaa 3600 ng Lys Tyr Glu 1200
caa gca aag Gln Ala Lys	aac atc tct cag o Asn Ile Ser Gln i 1205	gac ctg gag aag cag g Asp Leu Glu Lys Gln 1 1210	oct gcc cga gtc 3648 la Ala Arg Val 1215

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Cag aag cta aag gat tac gag gac ctc agg gaa gac atg aga gga aag Gln Lys Leu Lys Asp Tyr Glu Asp Leu Arg Glu Asp Met Arg Gly Lys 1265 1270 1275 1280	3840
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aca gcc gcg gaa gaa gct cta agg aga att ccc gcc atc aac cgg acc Thr Ala Ala Glu Glu Ala Leu Arg Arg Ile Pro Ala Ile Asn Arg Thr 1345 1350 1355 1360	4080
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aat gct gcc gct gac gcc acg gag gcc aag aac aag gcc cat gag gca Asn Ala Ala Ala Asp Ala Thr Glu Ala Lys Asn Lys Ala His Glu Ala	4176
1380 1385 1390	
gag agg atc gcc agc gcc gcg cag aag aat gcc acc agt acc aag gcg Glu Arg Ile Ala Ser Ala Ala Gln Lys Asn Ala Thr Ser Thr Lys Ala 1395 1400 1405	4224
gag agg atc gcc agc gcc gcg cag aag aat gcc acc agt acc aag gcg Glu Arg Ile Ala Ser Ala Ala Gln Lys Asn Ala Thr Ser Thr Lys Ala	4224 4272
gag agg atc gcc agc gcc gcg cag aag aat gcc acc agt acc aag gcg Glu Arg Ile Ala Ser Ala Ala Gln Lys Asn Ala Thr Ser Thr Lys Ala 1395 1400 1405  gac gca gaa aga acc ttc ggg gaa gtt aca gat ctg gat aat gag gtg Asp Ala Glu Arg Thr Phe Gly Glu Val Thr Asp Leu Asp Asn Glu Val	

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cag ctg gac aca gtg gac ctg aac aag ctc aat gag atc gaa ggc tcc 4512 Gln Leu Asp Thr Val Asp Leu Asn Lys Leu Asn Glu Ile Glu Gly Ser 1490 1495 1500
ctg aac aaa gcc aaa gac gaa atg aag gcc agc gac ctg gac agg aag 4560 Leu Asn Lys Ala Lys Asp Glu Met Lys Ala Ser Asp Leu Asp Arg Lys 1505 1510 1515 1520
gtg tct gac ctg gag agc gag gct cgg aag cag gaa gca gcc atc atg Val Ser Asp Leu Glu Ser Glu Ala Arg Lys Gln Glu Ala Ala Ile Met 1525 1530 1535
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gag gac atc aag aag acc cta cca acc ggc tgc ttc aac acc ccg tct 4704 Glu Asp Ile Lys Lys Thr Leu Pro Thr Gly Cys Phe Asn Thr Pro Ser 1555 1560 1565
atc gag aag ccc tagtggcgag agggctgtaa ggcagtgtcc ctgacagggg 4756 Ile Glu Lys Pro 1570
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<sup>&</sup>lt;210> 32

<sup>&</sup>lt;211> 1572

<sup>&</sup>lt;212> PRT

<sup>&</sup>lt;213> Mus musculus

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Thr	Сув	Gly 35	Thr	Pro	Pro	Glu	Glu 40	Tyr	Cys	Val	Gln	Thr 45	Gly	Val	Thr
Gly	Val 50	Thr	ГÀВ	Ser	Сув	His 55	Leu	Cys	Asp	Ala	Gly 60	Gln	Gln	His	Leu
Gln 65	His	Gly	Ala	Ala	Phe 70	Leu	Thr	qaA	Tyr	Asn 75	Asn	Gln	Ala	Авр	Thr 80
Thr	Trp	Trp	Gln	Ser 85	Gln	Thr	Met	Leu	Ala 90	Gly	Val	Gln	Tyr	Pro 95	Asn
Ser	Ile	Asn	Leu 100	Thr	Leu	His	Leu	Gly 105	Lув	Ala	Phe	Asp	Ile 110	Thr	туг
Val	Arg	Leu 115	Lys	Phe	His	Thr	Ser 120	Arg	Pro	Glu	Ser	Phe 125	Ala	Ile	Tyr
Lys	Arg 130	Thr	Arg	Glu	Asp	Gly 135	Pro	Trp	Ile	Pro	Tyr 140	Gln	Tyr	Tyr	Ser
Gly 145	Ser	Cys	Glu	Asn	Thr 150	Tyr	Ser	Lys	Ala	Asn 155	Arg	Gly	Phe	Ile	Arg 160
Thr	Gly	Gly	Asp	Glu 165	Gln	Gln	Ala	Leu	Cys 170	Thr	Asp	Glu	Phe	Ser 175	Asp
Ile	Ser	Pro	Leu 180	Thr	Gly	Gly	Asn	Val 185	Ala	Phe	Ser	Thr	Leu 190	Glu	Gly
Arg	Pro	Ser 195	Ala	Tyr	Asn	Phe	Asp 200	Asn	Ser	Pro	Val	Leu 205	Gln	Glu	Trp
Val	Thr 210	Ala	Thr	Asp	Ile	Arg 215	Val	Thr	Leu	Asn	Arg 220	Leu	Asn	Thr	Phe
Gly 225	Asp	Glu	Val	Phe	Asn 230	Asp	Pro	Lys	Val	Leu 235	Lys	Ser	Tyr	Tyr	Tyr 240
Ala	Ile	Ser	Asp	Phe 245	Ala	Val	Gly	Gly	Arg 250	Cys	Lys	Суз	Asn	Gly 255	His
Ala	Ser	Glu	Суя 260	Val	ГÀЗ	Asn	Glu	Phe 265	Asp	Lys	Leu	Met	Сув 270	Asn	Cys
Lys	His	Asn 275	Thr	Tyr	Gly	Val	Asp 280	Сув	Glu	Lув	Сув	Leu 285	Pro	Phe	Phe
Asn	Asp 290	Arg	Pro	Trp	Arg	Arg 295	Ala	Thr	Ala	Glu	Ser 300	Ala	Ser	Glu	Сув
Leu 305	Pro	Cys	Авр	Cys	Asn 310	Gly	Arg	Ser	Gln	Glu 315	Сув	Tyr	Phe	Asp	Pro 320

Glu Leu Tyr Arg Ser Thr Gly His Gly Gly His Cys Thr Asn Cys Arg 325 330 335

- Arg Leu Gly Asn Thr Glu Ala Cys Ser Pro Cys His Cys Ser Pro Val 355 360 365
- Gly Ser Leu Ser Thr Gln Cys Asp Ser Tyr Gly Arg Cys Ser Cys Lys 370 380
- Pro Gly Val Met Gly Asp Lys Cys Asp Arg Cys Gln Pro Gly Phe His 385 390 395 400
- Ser Leu Thr Glu Ala Gly Cys Arg Pro Cys Ser Cys Asp Pro Ser Gly 405 410 415
- Ser Thr Asp Glu Cys Asn Val Glu Thr Gly Arg Cys Val Cys Lys Asp 420 425 430 .
- Asn Val Glu Gly Phe Asn Cys Glu Arg Cys Lys Pro Gly Phe Phe Asn 435 440 445
- Leu Glu Ser Ser Asn Pro Lys Gly Cys Thr Pro Cys Phe Cys Phe Gly 450 455 460
- His Ser Ser Val Cys Thr Asn Ala Val Gly Tyr Ser Val Tyr Asp Ile 465 470 475 480
- Ser Ser Thr Phe Gln Ile Asp Glu Asp Gly Trp Arg Val Glu Gln Arg 485 490 495
- Asp Gly Ser Glu Ala Ser Leu Glu Trp Ser Ser Asp Arg Gln Tyr Ile
  500 505 510
- Ala Val Ile Ser Asp Ser Tyr Phe Pro Arg Tyr Phe Ile Ala Pro Val 515 520 525
- Lys Phe Leu Gly Asn Gln Val Leu Ser Tyr Gly Gln Asn Leu Ser Phe 530 540
- Ser Phe Arg Val Asp Arg Arg Asp Thr Arg Leu Ser Ala Glu Asp Leu 545 550 555 560
- Val Leu Glu Gly Ala Gly Leu Arg Val Ser Val Pro Leu Ile Ala Gln 565 570 575
- Gly Asn Ser Tyr Pro Ser Glu Thr Thr Val Lys Tyr Ile Phe Arg Leu 580 585 590
- His Glu Ala Thr Asp Tyr Pro Trp Arg Pro Ala Leu Ser Pro Phe Glu 595 600 605
- Phe Gln Lys Leu Leu Asn Asn Leu Thr Ser Ile Lys Ile Arg Gly Thr 610 615 620
- Tyr Ser Glu Arg Ser Ala Gly Tyr Leu Asp Asp Val Thr Leu Gln Ser 625 630 635 640
- Ala Arg Pro Gly Pro Gly Val Pro Ala Thr Trp Val Glu Ser Cys Thr

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Сув	Pro	Val	Gly 660	Tyr	Gly	Gly	Gln	Phe 665	Суз	Glu	Thr	Сув	Leu 670	Pro	Gly
Tyr	Arg	Arg 675	Glu	Thr	Pro	Ser	Leu 680	Gly	Pro	Tyr	Ser	Pro 685	Сув	Val	Leu
Суз	Thr 690	Сув	Asn	Gly	His	Ser 695	Glu	Thr	Сув	Asp	Pro 700	Glu	Thr	Gly	Val
Cys 705	Asp	Cys	Arg	Asp	Asn 710	Thr	Ala	Gly	Pro	His 715	Cys	Glu	Lys	Сув	Ser 720
Asp	Gly	Tyr	Tyr	Gly 725	Asp	Ser	Thr	Leu	Gly 730	Thr	Ser	Ser	Asp	Cys 735	Gln
Pro	Cys	Pro	Cys 740	Pro	Gly	Gly	Ser	Ser 745	Cys	Ala	Ile	Val	Pro 750	Lys	Thr
Lys	Glu	Val 755	Val	Cys	Thr	His	Cys 760	Pro	Thr	Gly	Thr	Ala 765	Gly	Lys	Arg
Cys	Glu 770	Leu	Cys	Asp	qaA	Gly 775	Tyr	Phe	Gly	Asp	Pro 780	Leu	Gly	Ser	Asn
Gly 785	Pro	Val	Arg	Leu	Cys 790	Arg	Pro	Cys	Gln	Суз 795	Asn	Asp	Asn	Ile	<b>Asp</b> 008
Pro	Asn	Ala	Val	Gly 805	Asn	Сув	Asn	Arg	Leu 810	Thr	Gly	Glu	Суз	Leu 815	Lys
Cys	Ile	Tyr	Asn 820	Thr	Ala	Gly	Phe	Tyr 825	Сув	qaA	Arg	сув	830 Lys	Glu	Gly
Phe	Phe	Gly 835	Asn	Pro	Leu	Ala	Pro 840	Asn	Pro	Ala	qaA	Lys 845	Суз	Lys	Ala
Сув	Ala 850	Cys	Asn	Tyr	Gly	Thr 855	Val	Gln	Gln	Gln	Ser 860	Ser	Сув	Asn	Pro
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Gly	Thr	Сув	Asp	Pro 885	Gly	Tyr	Tyr	Asn	Leu 890	Gln	Ser	Gly	Gln	Gly 895	Cys
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Сув	Glu 930	Arg	Сув	Glu	Thr	Asn 935	His	Phe	Gly	Phe	Gly 940	Pro	Glu	Gly	Сув
Lys 945	Pro	Сув	Asp	Cys	His 950	His	Glu	Gly	Ser	Leu 955	Ser	Leu	Gln	Cys	Lys 960

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Asp Gln Cys Glu Glu Asn Tyr Phe Tyr Asn Arg Ser Trp Pro Gly Cys 980 985 990

- Gln Glu Cys Pro Ala Cys Tyr Arg Leu Val Lys Asp Lys Ala Ala Glu 995 1000 1005
- His Arg Val Lys Leu Gln Glu Leu Glu Ser Leu Ile Ala Asn Leu Gly 1010 1015 1020
- Thr Gly Asp Asp Met Val Thr Asp Gln Ala Phe Glu Asp Arg Leu Lys 1025 1030 1035
- Glu Ala Glu Arg Glu Val Thr Asp Leu Leu Arg Glu Ala Gln Glu Val 1045 1050 1055
- Lys Asp Val Asp Gln Asn Leu Met Asp Arg Leu Gln Arg Val Asn Ser 1060 1065 1070
- Ser Leu His Ser Gln Ile Ser Arg Leu Gln Asn Ile Arg Asn Thr Ile 1075 1080 1085
- Glu Glu Thr Gly Ile Leu Ala Glu Arg Ala Arg Ser Arg Val Glu Ser 1090 1095 1100
- Thr Glu Gln Leu Ile Glu Ile Ala Ser Arg Glu Leu Glu Lys Ala Lys 1105 1110 1115 1120
- Met Ala Ala Asn Val Ser Ile Thr Gln Pro Glu Ser Thr Gly Glu Pro 1125 1130 1135
- Asn Asn Met Thr Leu Leu Ala Glu Glu Ala Arg Arg Leu Ala Glu Arg 1140 1145 1150
- His Lys Gln Glu Ala Asp Asp Ile Val Arg Val Ala Lys Thr Ala Asn 1155 1160 1165
- Glu Thr Ser Ala Glu Ala Tyr Asn Leu Leu Leu Arg Thr Leu Ala Gly 1170 1175 1180
- Glu Asn Gln Thr Ala Leu Glu Ile Glu Glu Leu Asn Arg Lys Tyr Glu 1185 1190 1195 1200
- Gln Ala Lys Asn Ile Ser Gln Asp Leu Glu Lys Gln Ala Ala Arg Val 1205 1210 1215
- His Glu Glu Ala Lys Arg Ala Gly Asp Lys Ala Val Glu Ile Tyr Ala 1220 1225 1230
- Ser Val Ala Gln Leu Thr Pro Val Asp Ser Glu Ala Leu Glu Asn Glu 1235 1240 1245
- Ala Asn Lys Ile Lys Lys Glu Ala Ala Asp Leu Asp Arg Leu Ile Asp 1250 1260
- Gln Lys Leu Lys Asp Tyr Glu Asp Leu Arg Glu Asp Met Arg Gly Lys 1265 1270 1275 1280
- Glu His Glu Val Lys Asn Leu Leu Glu Lys Gly Lys Ala Glu Gln Gln 1285 1290 1295

Thr Ala Asp Gln Leu Leu Ala Arg Ala Asp Ala Ala Lys Ala Leu Ala 1300 1305 1310

- Glu Glu Ala Ala Lys Lys Gly Arg Ser Thr Leu Gln Glu Ala Asn Asp 1315 1320 1325
- Ile Leu Asn Asn Leu Lys Asp Phe Asp Arg Arg Val Asn Asp Asn Lys 1330 1335 1340
- Thr Ala Ala Glu Glu Ala Leu Arg Arg Ile Pro Ala Ile Asn Arg Thr 1345 1350 1355 1360
- Ile Ala Glu Ala Asn Glu Lys Thr Arg Glu Ala Gln Leu Ala Leu Gly
  1365 1370 1375
- Asn Ala Ala Asp Ala Thr Glu Ala Lys Asn Lys Ala His Glu Ala 1380 1385 1390
- Glu Arg Ile Ala Ser Ala Ala Gln Lys Asn Ala Thr Ser Thr Lys Ala 1395 1400 1405
- Asp Ala Glu Arg Thr Phe Gly Glu Val Thr Asp Leu Asp Asn Glu Val 1410 1415 1420
- Asn Gly Met Leu Arg Gln Leu Glu Glu Ala Glu Asn Glu Leu Lys Arg 1425 1430 1435 1440
- Lys Gln Asp Asp Ala Asp Gln Asp Met Met Ala Gly Met Ala Ser 1445 1450 1455
- Gln Ala Ala Gln Glu Ala Glu Leu Asn Ala Arg Lys Ala Lys Asn Ser 1460 1465 1470
- Val Ser Ser Leu Leu Ser Gln Leu Asn Asn Leu Leu Asp Gln Leu Gly 1475 1480 1485
- Gln Leu Asp Thr Val Asp Leu Asn Lys Leu Asn Glu Ile Glu Gly Ser 1490 1495 1500
- Leu Asn Lys Ala Lys Asp Glu Met Lys Ala Ser Asp Leu Asp Arg Lys 1505 1510 1515
- Val Ser Asp Leu Glu Ser Glu Ala Arg Lys Gln Glu Ala Ala Ile Met 1525 1530 1535
- Asp Tyr Asn Arg Asp Ile Ala Glu Ile Ile Lys Asp Ile His Asn Leu 1540 1545 1550
- Glu Asp Ile Lys Lys Thr Leu Pro Thr Gly Cys Phe Asn Thr Pro Ser

Ile Glu Lys Pro 1570

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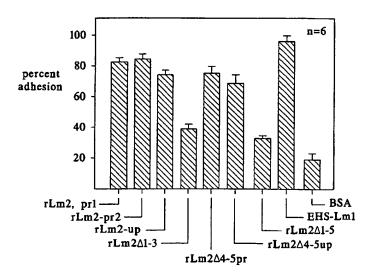
(71) Applicant (for all designated States except US): UNI-VERSITY OF MEDICINE AND DENTISTRY OF NEW JERSEY ROBERT WOOD JOHNSON MEDI-CAL SCHOOL [US/US]; Piscataway, NJ 08854 (US).

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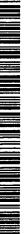
(54) Title: LAMININ 2 AND METHODS FOR ITS USE

#### C2C12 myoblasts



Substrate (5 µg/ml)

(57) Abstract: The present invention provides substantially purified laminin 2, methods for making recombinant laminin 2, cells that express recombinant laminin 2, and methods for using the substantially purified laminin 2 to accelerate peripheral nervous system nerve regeneration, and to promote cell attachment and migration.



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#### INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/12 C12N15/62 C12N5/10 C07K14/78 A61K38/39 A61L31/00 A61P9/00 A61P21/00 A61P25/00 According to International Patent Classification (IPC) or to both national classification and IPC B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal C. DOCUMENTS CONSIDERED TO BE RELEVANT Relevant to claim No. Citation of document, with indication, where appropriate, of the relevant passages Category \* 30-33 X WO 95 08628 A (JOLLA CANCER RES FOUND) 30 March 1995 (1995-03-30) SeqIdNo.4: 100.0% identity in 3098 aa 16-18, Y overlap with SeqIdNo.2 / 99.8% identity in 22-24. 28,29 9535nt overlap with SeqIdNo.1 claims 14-16,18,30,33; figure 6 UTANI A ET AL: "A specific sequence of 1-15 X the laminin alpha 2 chain critical for the initiation of heterotrimer assembly" JOURNAL OF BIOLOGICAL CHEMISTRY., vol. 270, no. 7, 17 February 1995 (1995-02-17), pages 3292-3298, XP002153607 16-18, Y figure 4 22-24, 28.29 -/--Further documents are listed in the continuation of box C. Patent family members are listed in annex. X Special categories of cited documents: "I tater document published after the international filing date or priority date and not in conflict with the application but clied to understand the principle or theory underlying the "A" document defining the general state of the art which is not considered to be of particular relevance invention "E" earlier document but published on or after the international "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such docu-ments, such combination being obvious to a person skilled O document referring to an oral disclosure, use, exhibition or other means document published prior to the international filling date but "&" document member of the same patent family later than the priority date claimed Date of the actual completion of the international search Date of mailing of the international search report 8 December 2000 22/12/2000 Authorized officer Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo ni, Lonnoy, O Fax: (+31-70) 340-3016

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Y	TALTS J ET AL: "Structural analysis and proteolytic processing of recombinant 6 domain of mouse laminin alpha2 chain" FEBS LETTERS., vol. 426, no. 1, 10 April 1998 (1998-04-10), pages 71-76, XP002153608 figure 1B	30-33	
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## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-29 (all totally) and 34 (partially)

Laminin 2, materials and methods for its recombinant production, and applications thereof.

2. Claims: 30-33 (all totally) and 34 (partially)

Laminin alpha 2 chain consisting of the sequence SeqIdNo.1-2, and application thereof.

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